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Bjerre Bengt and Åstedt Birger Acta obst et gynec scandinav 43 1 1964

From the Department of Obstetrics and Gynæcology (Professor Stig Kullander) Malmo General Hospital Malmo Sweden

MATERNAL MORTALITY IN SWEDEN

BY

BENGT BJERRE AND BIRGER ÅSTEDT

The maternal mortality in Sweden, as in most other countries, has fallen progressively during the last few decades In this paper, which is concerned with an analysis of the maternal mortality at Swedish hospitals during a 6 year period (1956–61), it would have been informative to compare the results with the rates for other countries But most publications of foreign series on record are based on observations made at a single department of obstetrics and are then either too small to warrant comparison or they span too long a period, during which the mortality may have varied too much to allow strict comparison with that found in the present investigation Moreover different countries have used different classifications Like the WHO most countries do not give deaths in association with abortion as a separate group but include them under the heading of maternal mortality In U S A all deaths, that occur within 3–12 months of parturition according to the state are registered under the heading of maternal mortality irrespective of their cause In most series the proportion of cases with *post mortem* verification of the cause of death is small

The WHO gives the mortality as the number of deaths per 100 000 live births but many countries adopt other classifications The *Svenska Statistiska Centralbyran* (The Registrar General for Sweden) uses largely the same classification as WHO Table I compares the maternal mortality in Sweden with that in some other countries

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Table II *Percentage Distribution of Institutional and Domiciliary Deliveries (Sveriges officiella statistik Halso- och sjukvard)*
Institutional Deliveries

	Type I	Type II	Type III	Domiciliary Deliveries
1950	45 6	41 4	7 1	5 9
1955	59	33 3	5 3	2 4
1960	67 3	30 8	1 3	0 6

Type I Under supervision of a specialist in obstetrics
II Not necessarily under supervision of a specialist in obstetrics
III Doctor present only exceptionally

Table III *Maternal Mortality in Institutes of Types I II and III 1956—1960*

Type of institution	I	II	III	Domiciliary Deliveries
Number of deliveries	335 286	173 340	14 800	5 877
Number of deaths	96	56	4	3
Deaths per 100 000 live births	28 6	32 3	27 0	51 0

Type I Under supervision of a specialist in obstetrics
II Not necessarily under supervision of a specialist in obstetrics
III Doctor present only exceptionally

conditions under which women in Sweden are delivered is apparent from Table II

The frequency of domiciliary deliveries and deliveries in small maternity departments (type III) is almost nil More and more hospitals are being expanded to include a special department of obstetrics under the supervision of specially trained obstetricians More than two thirds of all deliveries occur at such departments, which are called Type I departments of obstetrics The number of deliveries and the maternal mortality in the different types of departments and in the mother s homes for the 5 year period (1956-60) are given in Table III (figures obtained partly from the Annual Reports of the Royal Medical Board) The mortality is significantly lower in special departments of obstetrics (type I) than in type II, which often lack specially trained obstetricians The figures for type III departments and domiciliary deliveries during this period are too small to warrant any conclusions

Table I *Maternal Mortality in Some Countries since 1936 Deaths per 100 000 Live Births* (According to Epidemiological and Vital Statistics Report, WHO 1960)

Country	Average Annual Number			1956	1957	1958
	1936-38	1947-49	1953-55			
Austria	541	229	116	122	90	89
Denmark	350	106	65	48	41	44
England and Wales	338	109	71	57	48	44
Finland	490	181	115	111	89	100
France	206	87	67	55	57	55
Italy	272	157	134	119	114	111
Norway	268	115	68	60	51	54
Sweden	283	76	55	34	36	30
Switzerland	435	173	112	75	76	75
West Germany	—	203	159	136	125	118
Columbia	839	463	383	311	292	288
United Arabian Republic	424	174	123	103	113	—
Japan	255	168	181	170	171	155
New Zealand	380	113	50	40	67	41
USA (All races)	496	114	53	41	41	38

1948—1949
Data not available

In the annual reports of the Royal Medical Board in Sweden (Sveriges officiella statistik Hälso- och Sjukvard) maternal mortality includes deaths *after* delivery* irrespective of the direct cause of death, as well as deaths of puerperal women who have been transferred to other departments and died there We adopted this procedure in the present investigation but also included women admitted to the department of obstetrics for delivery and who died there *before* parturition

The maternal mortality is lowest in those countries and districts where most women are delivered at large departments of obstetrics or maternity homes (Simon, 1955 Kaern, 1958 Dubuis and Zenklusen, 1959 and Sjovall 1961) In Sweden the percentage of mothers delivered in hospital has successively increased The change that has occurred during the 1950 s in the

* *Delivery* Birth of reportable fœtus, i e shown signs of life or if stillborn a length of at least 35 cm

three cases not treated with oxytocin It is not possible to decide whether the uterine rupture was produced by the oxytocin, by the forceps or whether it had occurred previously and produced symptoms that had indicated medication with oxytocin or forceps delivery

The material included 10 cases of *afibrinogenæmia* This complication was probably precipitated by atony in one case, by an amniotic embolus in one and by premature detachment of the placenta in two In six other cases hypofibrinogenæmia or afibrinogenæmia appears to have been a contributory cause, but these cases were allocated under the diagnosis of *placenta prævia accreta, uterine atony and amniotic embolus* The patients were treated with fibrinogen, blood transfusions and Dextran Epsilon aminocaproic acid was not used in any of these cases In some patients in which the blood loss could not always be completely compensated by blood transfusions, large supplementary doses of Dextran were given Thus, one patient was given seven bottles of Dextran and only six bottles of whole blood

In five deaths from *postoperative hæmorrhage* and in three because of *cervical rupture* and *vaginal rupture* (Table IV) it would appear that the initial loss of blood was underestimated and blood transfusion was therefore delayed As a matter of fact difficulty in obtaining blood for transfusions appeared to contribute to many of the 40 deaths It seems that it was not the rule to ascertain the blood groups of the patients at the antenatal clinics except regarding Rh system

The distribution of the deaths among the various diagnoses is given in Table V

Toxæmia of pregnancy was responsible for 12 deaths Of these, seven were multiparæ including two who had had toxæmia of pregnancy in association with a previous pregnancy and two who had essential hypertension Of the primiparæ, one had diabetes In most cases antenatal care had been satisfactory But two of the mothers had not even been examined during pregnancy until admission for delivery In eight cases hypotensive drugs had been given usually Ne Hi Pe by intravenous drip according to Arfwedsson (1955) and consisting of glucose solution with 25 mg Nepresolin (CIBA) 50–100 mg Hibernal (LEO) and 50–200 mg

Material and Methods

The investigation is based on an analysis of the hospital records and autopsy reports of the mothers who died within the 6 year period at the departments of obstetrics in Swedish hospitals. The hospital records were kindly placed at our disposal by the heads of the various departments in question. During this period 407,340 women were delivered, and 110 deaths occurred. Necropsy was performed in 91 cases and histopathological examination in 79 of these. Several of the patients showed evidence of more than one complication, but they were all classified according to the one that appeared to be the main cause of death.

Results

The commonest cause of death was hæmorrhage (Table IV), which was noted in 40 of the 110 cases.

Uterine rupture occurred in 11 of the cases with hæmorrhage and required laparotomy in a further 4, all of whom afterwards died from postoperative peritonitis with ileus. In one of the 15 cases the scar after Cæsarean section (transverse incision of isthmus) ruptured. In the other cases the obstetric histories contained nothing suggesting factors predisposing to uterine rupture. All of the women were multiparæ, and all had previously borne children at full term. In four cases the infant was delivered by podalic version and extraction. In six cases oxytocin had been given. In one of these delivery was completed by vacuum extraction and in two by forceps. Delivery had also been completed by forceps in the

Table IV. *Distribution of Hæmorrhages among Complications (Departments of Obstetrics) 1956—1961*

Uterine rupture	11 (+4)
Afibrinogenæmia	10 (+6)
Postoperative bleeding	5
Cervical / vaginal rupture	3
Uterine atony	3
Placenta prævia et accreta	1
Uterine inversion	1
Other hæmorrhages	6
Total	40

three cases not treated with oxytocin It is not possible to decide whether the uterine rupture was produced by the oxytocin, by the forceps or whether it had occurred previously and produced symptoms that had indicated medication with oxytocin or forceps delivery

The material included 10 cases of *afibrinogenæmia* This complication was probably precipitated by atony in one case, by an amniotic embolus in one and by premature detachment of the placenta in two In six other cases hypofibrinogenæmia or afibrinogenæmia appears to have been a contributory cause, but these cases were allocated under the diagnosis of *placenta prævia accreta uterine atony and amniotic embolus* The patients were treated with fibrinogen, blood transfusions and Dextran Epsilon aminocaproic acid was not used in any of these cases In some patients in which the blood loss could not always be completely compensated by blood transfusions large supplementary doses of Dextran were given Thus one patient was given seven bottles of Dextran and only six bottles of whole blood

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Table V *Causes of Death 1956—1961 (Departments of Obstetrics)*

Hæmorrhage	40
Toxæmia	12
Genital infection	7
Other infections	5
Embolus (pulm)	5
Anæsthesia	3
Ileus	6
Amniotic embolus	8
Air embolus	4
Heart disease	4
Cancer	4
Miscellaneous	12
Total	110

Pethidine Only 1 patient was treated by the method of Stroganoff Two patients with anuria and uræmia were referred to a special department for renal diseases for dialysis, and died there

Genital tract infection was noted in five cases of post operative pelvic abscess and peritonitis including one case in which extra-uterine pregnancy went on to term In two cases premature rup ture of the membranes was largely responsible for the infection No instance of classical puerperal sepsis was seen Nor was any infection noted after manipulations *per vaginam* such as manual removal of the placenta

Two cases of pneumonia and one case of peritonitis secondary to appendicitis were recorded in the group miscellaneous infections , which also embraces such a rare condition as acute infectious hæmorrhagic gastritis with perforation and peritonitis

Thromboembolism occurred in only 5 cases Three of these patients had slight toxæmia of pregnancy and 1 patient had a heart disease They were first bedridden for some weeks and then died from lung embolism without any clinical evidence of throm bosis None of these patients had been operated upon The fifth patient had an open foramen ovale and died from cerebral embolism

Anæsthesia might have been a contributory cause in some cases of hæmorrhage in which it was necessary to anæsthetize the pa tient, but otherwise anæsthesia was the main cause of death in

only three cases In all of these the open mask technique had been used and no anæsthetist had been present.

Postoperative ileus was the cause of six deaths All of these patients had some degree of peritonitis but fluid balance disturbances appear to have been the main causes of the fatal issue

We ascribed eight cases to *amniotic embolism,* including six verified histopathologically In three of the cases there was hypofibrinogenæmia *Air embolism* was considered the certain cause of death in 2 and the probable cause in 2 others

The 4 patients in whom *heart complications* were the main cause of death also had obstetrical complications Four patients had *malignant tumours* and in these it is doubtful whether the pregnancy had anything to do with the fatal course

The group *other deaths* included 2 cases of ruptured cerebral aneurysm and 1 case each of ruptured aortic aneurysm, essential hypertension with cerebral hæmorrhage, cronic nephritis, diabetes, acute pancreatitis, ulcerative enteritis cerebral insult of unknown origin, psychosis of pregnancy with suicide, pulmonary hæmorrhage of unknown cause and one completely obscure case

Discussion

In an attempt to elucidate the fall in the total maternal mortality since 1930 and the change in the various diagnostic groups this material was compared with the data given in a previous similar investigation made in departments of obstetrics in Swedish hospitals in 1930–1935, when 245 deaths occurred per 82,403 deliveries and from 1950–1955, when 177 deaths occurred among 343,182 deliveries (Bjerre 1958) The numbers of deaths in the various diagnostic groups are given per 100 000 deliveries in Table VI

The frequency of deaths from hæmorrhage fell substantially from 1930 to 1950 after which it remained *fairly stationary* But the mortality from toxæmia of pregnancy fell successively even during the 1950 s It appears that an abrupt fall occurred at the end of 1955 This was when the most of the Swedish *departments of* obstetrics started a joint campaign against eclampsia i e treatment of eclampsia with Nepresolin Hibernal Pethidine by intravenous drip (See Arfwedson, 1955) while many of the re-

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death , it might be mentioned that four deaths were due to diabetes during the first half of the 1950 s, against only one during the latter half

The total mortality has fallen considerably

Since 1957 the annual returns of the departments of obstetrics in Swedish hospitals also give the to al number of women delivered by Cæsarean section The frequency has remained fairly steady, about 1 9 per cent of the total number of deliveries Assuming this percentage to hold also for 1956 7,700 of 407,700 mothers would have been delivered by Cæsarean section Of the women delivered by Cæsarean section in the present material, 36 died This implies a frequency of about 0 47 per cent Many of them were poor surgical risks In 17 cases there was no reason to regard the operation *per se* as responsible for the fatal issue, but in 10 cases Cæsarean section was possibly responsible for the fatal issue As to the remaining nine patients, all seemed to be in good general condition before the operation and they all died from postoperative complications, four from postoperative hæmorrhage and five from ileus

The decrease found in the maternal mortality is probably due to several factors such as the advent of sulphonamides and antibiotics, dicumarol and heparin advances in cardiology improved anæsthetic methods and modern transfusion techniques The free antenatal clinics have probably contributed considerably to the suppression of the frequency of toxæmia of pregnancy In addition toxæmias of pregnancy are now treated more effectively with modern diuretics and hypotensive drugs

Hæmorrhage is still the commonest cause of death and is responsible for more than one third of all maternal deaths in Swedish hospitals The introduction of transfusion therapy was followed by an abrupt fall in the frequency of deaths from hæmorrhage but no further improvements has occurred since 1950 The onset of hæmorrhage is usually sudden and immediate treatment is obviously imperative *i e* all blood lost should be replaced by infusion of whole blood whilst elimination of the cause of bleeding In order to enable this without delay antenatal care should include classification not only according to Rh factor but also to the ABO

Table VI *Number of Deaths, Classified According to Cause per 100 000 Deliveries (Departments of Obstetrics)*

	1930–1935	1950–1955	1956–1961
Hæmorrhage	42	11	10
Toxæmia	46	17	3
Genital infection	97	2	2
Other infections	39	2	1
Embolus (pulm.)	31,5	2.5	1
Anæsthesia	1	2	0.5
Ileus	8.5	2.5	1,5
Amniotic embolus	1	1	2
Air embolus	0	1	1
Heart disease	13	4	1
Cancer	4	2	1
Miscellaneous	5	4.5	3
Total	297	51,5	27

maining departments tried other similar preparations. Though the overall frequency of toxæmia of pregnancy decreased, Ne Hi Pe appears to have been mainly responsible for the reduction of the mortality from toxæmia of pregnancy.

The number of deaths from infections and emboli has fallen progressively for well known reasons.

The number of deaths ascribable to anæsthesia has always been low in Sweden, but it nevertheless fell still more during the 1950's. The presence of an experienced anæsthetist at every obstetric operation is invaluable. Intervention is often indicated because of hæmorrhage and the patient is then commonly in poor condition for the induction of anæsthesia, which therefore makes the assistance of an anæsthetist particularly desirable.

The mortality from ileus has fallen and will probably fall still more with improvements in the control of the fluid balance. New therapeutic methods, *e.g.* with hydrocortisone *i.v.* has already improved the situation and there is reason to hope that intimate cooperation with the surgeons and anæsthetists will reduce the number of deaths from ileus still more.

The number of deaths from amniotic embolus appears to have increased, but this increase may be only apparent and due to improved diagnostic methods. As to the group other causes of

death, it might be mentioned that four deaths were due to diabetes during the first half of the 1950 s, against only one during the latter half

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The decrease found in the maternal mortality is probably due to several factors such as the advent of sulphonamides and antibiotics, dicumarol and heparin advances in cardiology, improved anæsthetic methods and modern transfusion techniques The free antenatal clinics have probably contributed considerably to the suppression of the frequency of toxæmia of pregnancy In addition toxæmias of pregnancy are now treated more effectively with modern diuretics and hypotensive drugs

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Anæsthesia	1	2	0 5
Ileus	8 5	2,5	1 5
Amniotic embolus	1	1	2
Air embolus	9	1	1
Heart disease	13	4	1
Cancer	4	2	1
Miscellaneous	5	4 5	3
Total	207	51 5	27

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In recent years hypofibrinogenæmia has been treated effectively with fibrinogen and epsilon aminocaproic acid and these preparations will surely help to suppress the maternal mortality still more

SUMMARY

The maternal mortality is lower in Sweden than in most other countries This is due in part to the fact that most women in Sweden are delivered in hospitals (over 99 per cent in 1960) During the 1950's the number of departments of obstetrics under the direction of a trained specialist has increased considerably At present 67 per cent of all children are born at such departments In these departments the maternal mortality is lower than elsewhere

The hospital records of departments of obstetrics in Swedish hospitals for the years 1956–1961 were searched for maternal deaths and the results were analysed and compared with similar figures for the years 1930–1935 and 1950–1955 The maternal mortality was found to have decreased considerably in all diagnostic groups The most important improvement noted since 1950 was the fall in the frequency of toxæmia of pregnancy from the former to the latter half of the 1950's it decreased from 17 to three per 100,000 deliveries It is noteworthy that the number of deaths from hæmorrhage has hardly decreased since 1950 and that practically every third death is due to hæmorrhage The possibilities of reducing the maternal mortality still more are discussed

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THERAPEUTIC ABORTION AND STERILIZATION IN DIABETIC PATIENTS

BY

EBBE BRANDSTRUP MOGENS OSLER and JØRGEN PEDERSEN

Therapeutic abortion or sterilization is not indicated in patients with uncomplicated diabetes mellitus, but these procedures are sometimes indicated in patients with late vascular complications of diabetes in cases where the disease is likely to be inherited, and in a few other special circumstances

Admittedly a discussion of these problems on an international basis is difficult because of the wellknown differences in religion, ethics and trad tion, hence in reviews on diabetes and pregnancy the indications for therapeutic abortion or sterilization are very sparsely discussed Given *et al* (1950) White (1952), Reis *et al* (1952) Katsch (1960) and Hagbard (1961) and as far as we are aware a detailed discussion has not been published

It is the aim of this paper to show how these problems have been dealt with in this department according to the laws and medical views of our country

The Laws

The legal basis for evaluation of the indications has been our so called pregnancy law of 1937 and later the pregnancy law of 1956 No major change in the indications during the period of investigation has taken place

The law of 1956 says "A woman may have her pregnancy interrupted when this is necessary to avert serious danger to the woman s life or health In the assessment of this danger account should be taken of the conditions under which the woman must

system In addition, there must be a blood bank near the department of obstetrics

In recent years hypofibrinogenæmia has been treated effectively with fibrinogen and epsilon aminocaproic acid and these preparations will surely help to suppress the maternal mortality still more

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operations has increased somewhat in the later years, mostly due to a larger number of patients with severe disease applying to the Department, including patients sent for evaluation of an indication for abortion and sterilization Most patients were between 20 and 40 years old, only one less than 20 and 4 more than 40 years The 71 patients had 146 previous pregnancies, but they had only 70 living children Only 4 had three children none had more

The Indications

In evaluation of the patients condition we have had the help of other departments of the hospital and special institutes for example the opthalmological department the psychiatric department, the University Institute of Eugenics and, for the social problems, the Mother s Aid Institution

Table II shows our indications, divided into subgroups with the number of cases in each group A few comments will be given in the discussion

Table II *Indications*

	Therap ab	Sterilization
MEDICAL INDICATION		
1 Diabetic nephropathy and/or prolif retinopathy	28	12
2 Diabetes complicated by non-diabetic disease		
A Heart disease	1	0
Chronic hepatitis	1	0
Hyperemesis	1	0
B Depression or anxiety neurosis	2	0
C Psycho somatic asthenia	14	8
D Bad obstetric history	8	4
E Bad social conditions	3	0
EUGENIC INDICATION	5	1
COMBINED (three or more indications)	4	0
Unknown (case notes lost)	0	1
TOTAL	74	28

Technique

Table III shows the technique for interruption of the pregnancies In most cases we were able to do a simple dilatation

live, and consideration must be given, not only to somatic and mental disease but also to somatic and psychical weakness.' Next the law says "A woman may have her pregnancy interrupted when there is a considerable risk that the child, owing to inherited factors or to damage or disease occurring during foetal life will suffer from mental disease, imbecility, other severe mental derangements, epilepsy, serious and incurable abnormality or bodily disease.' This is the eugenic indication. A following paragraph says that a woman may have her pregnancy interrupted in special cases where physical or mental defects or other medically founded circumstances make her unable to take care of her child'.

As to sterilization there is no law regarding the medical indications. The doctor is free to do what he thinks is medically justified. But there is a law concerning sterilization on social and eugenic indications. The former may be done only after application to and the consent of the Ministry of Justice.

Material

Table I shows our material, *i.e.* all diabetic women, who have been submitted to therapeutic abortion and/or sterilization from 1954–1962 inclusive. Therapeutic abortion has been performed 74 times on 71 patients and in 19 of these patients sterilization was carried out at the same time. Sterilization was performed on a further 9 patients giving altogether 28 sterilizations. The material, thus comprising 80 patients is divided in two periods, 1954–1959 and 1960–1962. The total number of deliveries was 283 in the first period and 171 in the second (infants weighing 1000 grams or more). It appears that the frequency of the

Table I. *Deliveries, Therapeutic Abortions and Sterilizations in Diabetic Patients 1954—1962 incl.*

	Deliveries		Therapeutic Abortions		Sterilizations	
	No.	Average per year	No.	Average per year	No.	Average per year
1954—1959	283	47.2	40	6.7	10	1.7
1960—1962	171	57.0	34	11.3	18	6.0
1954—1962	454	50.5	74	8.2	28	3.1

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Table III *Methods for Interruption of the Pregnancies*

Method	No of cases
Dilatation (Hegar) and evacuation	48
Dilatation (Hegar) laminaria tent and evacuation	3
Injection, evacuation	7
Abdominal hysterotomy	16
Total	74

and curettage, which means that the patients in this series came for investigation and treatment early, being aware of the potential danger of the pregnancy Twelve pregnancies were more than 12 weeks old (three more than 16 weeks) In seven cases we injected some substance (formalin, cremor saponis or glucose) intra- or extra-ovularly to bring about spontaneous evacuation, after which a curettage was done Hysterotomy was performed 16 times, in 15 of these cases we sterilized the patient at the same occasion For sterilization we used the Madlener method (crushing and ligation of a loop of the tubes) We had no deaths, no dangerous complications and very few minor ones a few very slight elevations of temperature, a few subsequent moderate uterine hæmorrhages, one hæmatoma in the parametrium and one hæmatoma in the rectus muscle

Comments and Discussion

Table II shows that the most frequent indication for operation was the presence of diabetic nephropathy This term includes any form of nephropathy accompanied by permanent proteinuria detected before or, in a few cases, in the first months of pregnancy, these patients are typical class F patients according to White's grouping (White, 1952) This complication involves increased risks for the mother during pregnancy because of the great frequency of superimposed preeclampsia Further we fear that the nephropathy will deteriorate faster when the patient goes through one or more pregnancies than if she does not but this we cannot prove, lacking comparable series of group F patients with and without pregnancies, observed through several years However, we cannot deny that we have been influenced by the perinatal mortality of 50 per cent in our series of 24

Table IV *Outcome of the Pregnancies in 24 Diabet c Pat ents in Group F*

		Infants	
		Dead	Live
Previous pregnancies	35	33	2
(Mostly treated in other clin cs)			
Pregnancies 1954—1962	24	13	11
(Royal Matern ty Dep B)			
(ante partum death 6 post partum death 7)			
Total		46	13

group F patients (Table IV) These poor results were not due to lack of care because a third of the 24 patients spent nearly the whole pregnancy in the department and only 3 of the 8 infants survived It should be noted too that the outcome of the 59 pregnancies in these women was 13 surviving babies or about 20 per cent

Although it is not clearly stated in our laws that the risk of having a dead baby should be considered no doubt the woman s attitude to the problem is very much dependent on the answer to her question What is my chance of having a live baby? and this applies to nurses and doctors as well The situation may be this for example a juvenile diabetic with nephropathy and other signs of late diabetic complications previously having lost 2 infants in late pregnancy and now in her third pregnancy The outlook is this at present she has to stay in the ward most of pregnancy she will have some degree of toxæmia and the risk of having a dead baby is 50–75 %

Some patients whom we have advised to have abortion induced have demanded to go through pregnancy and naturally we have given our help of these less than one half had a surviving baby

Our conclusion and conviction is that induced abortion and sterilization is indicated and legally justifiable in many cases belong ng to White s group F especially when the patient has gone through one or more pregnancies without success We will perform an induced abortion if the patient agrees However if the patient fully understands the prognosis and still wants to take the small chance of having a living baby it is justified to let her continue w th the pregnancy

The few cases in subgroup 2 A and 2 B (Table II) need no *comments because the diabetic condition* was of minor importance in recommending operation The subgroup 2 C comprises a *characteristic type of patient and situation* The patient is a juvenile diabetic, slim, nervous with very little physical and psychical strength, "brittle in *every respect Her capacity may* be fully occupied by maintaining her home and bringing up her (as a rule 2) children besides giving her chronic disease daily care Both she and we know that a real danger exists that a third baby will soon be too heavy a burden for her and a break-down will follow We feel that her strength must be preserved for her present family in the years to come Also we have to take into consideration the cooperation of the patient If she is non-cooperative and apt to neglect her treatment her personal risk is increased *Furthermore* other conditions and diseases—by themselves not strong enough to motivate an indication—may *favour an indication for abortion*

However, it should be stated that very often in such cases the initiative for having an abortion performed stems from the patient or her surroundings including her personal doctor Therefore, it should be stressed that in several such cases we have found no indication for abortion

Subgroup 2 D This group comprises patients who have had repeated Caesarean sections, severe pre-eclampsia and still births, or a new pregnancy before full recovery after a complicated delivery

Subgroup 2 E In three cases only the social conditions were the *dominating factors For example an unmarried woman living* alone in the countryside, in a rented room, neglecting her disease without the mental, physical and economic power to go through a complicated pregnancy and to take proper care of a child However, the social problems are considered in every case and these often play a part albeit a small one

Eugenic and medico-eugenic indications A pregnancy may be interrupted for purely eugenic reasons when *the disease is present* also in the father or in several near relations, or if the couple have had already one diabetic child *More often* there is a eugenic factor in support of a medical indication which is not sufficient

by itself, for example a strong history of diabetes, especially juvenile, in the mother's family

Although we have placed 4 cases only under the heading combined (Table II), meaning that each of for example a late diabetic, obstetrical, social and eugenic condition might be severe or nearly severe enough for inducing an abortion it should be recognised that the indications in most subgroups are multiple but the listed one is dominant

Generally we advise diabetics to have 2 children and we are extremely reluctant to interrupt pregnancy in a woman with no or one child only The fact that nevertheless we have performed the operation in such diabetics indicates the seriousness with which we have considered the risks and prognosis of these women With some relief we have noticed that operations have been performed without complications

From an ethical, emotional and surgical point of view therapeutic abortion is an evil If the treating doctors more often and more energetically would recommend contraception in the right cases much suffering could be avoided

SUMMARY

The indications for therapeutic abortion and sterilization in 74 abortions and 28 sterilizations performed in 80 diabetic patients during the period 1954–1962 are detailed

The main indication (28 induced abortions and 12 sterilizations) was late diabetic nephropathy (cases belonging to White's group F) A description of a special group of women with psychosomatic asthenia is given In 14 such cases abortion was induced

The operations were performed without deaths or major complications and even the minor complications were very few

There is a very strong case for 'planned parenthood' in diabetics

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ACHALASIA OF THE ŒSOPHAGUS IN ASSOCIATION WITH PREGNANCY

BY

A OLAVI KARJALAINEN

Achalasia of the cardia or cardiospasm seems to occur very infrequently in association with pregnancy A search of the literature has disclosed only a few reports Roques (1932) described two patients in whom symptoms of achalasia had already appeared before the onset of pregnancy Lindert (1956) reported one case with onset of symptoms during the first trimester of pregnancy The most recent contribution is by Stroup (1961), whose patient first showed symptoms during the second trimester

Other lesions of the œsophagus, such as hiatus hernia, œsophagitis, œsophageal peptic ulcer and stricture, are much more common in pregnancy and have been reported more frequently Vinson (1921, 1923) described 9 patients in whom œsophageal stricture had developed during pregnancy His observations regarding the occurrence of dysphagia during the last trimester drew the attention of physicians to the possibilty of œsophageal disease in conjunction with pregnancy Scott and Deutsch (1956) published a series comprising 34 patients in whom severe œsophagitis was diagnosed in the course of pregnancy In 25 of these a stricture developed in the distal portion of the Oesophagus Hiatus hernia seems to be fairly common in pregnant women Rennie, Land and Park (1949) published a paper on 31 cases of short œsophagus 5 of these associated with pregnancy The same association has since been dealt with by Sutherland *et al* (1956) and by Mixon and Woloshin (1956)

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In the cases reported by Lindert and by Stroup the course of pregnancy was seriously disturbed by achalasia, yet each of these patients was delivered of a viable fœtus In one of the two cases presented by Roques pregnancy had to be terminated in the fifth month because of progressive deterioration of the patient's condition The other patient was delivered spontaneously at the beginning of the eight month It is evident that achalasia is a grave complication of pregnancy In view of this the following case seems to merit publication

Case report

T J a married woman, aged 23 was first seen in the Outpatient department of the hospital on Dec 19 1960 She complained of difficulty in swallowing She had always been healthy and had had two normal deliveries in 1956 and 1959 During the latter of these pregnancies she had had slight difficulty in swallowing but had paid no attention to this She had been free from symptoms for nearly one year after delivery Since September 1960 she had suffered constantly from dysphagia which increased in severity Occasionally a burning pain was felt beneath the sternum She lost 7 kilograms in weight over a period of six months X ray examination made elsewhere on Dec 12 1960, showed marked distension of the œsophagus and this was why the patient was referred to the hospital Her general condition was good. Physical examination of the heart and lungs revealed nothing of special importance On œsophagoscopy, Dec 27 the œsophageal wall was found to be smooth The œsophagus was moderately dilated above the cardia, but narrowed abruptly at the level of the cardia The œsophagoscope could not be passed through the cardia Dilatation of the œsophagus was started, 11 dilatations being performed over a period of three months Following each bougienage the patient was able to swallow normally for a few days but then had to stop taking solid food After 3 months treatment the otologist suggested operation Oesophagoscopy was repeated on April 27 1961 the region of the cardia was not narrow on the contrary it was wider than usually The œsophageal mucosa was entirely normal

On œsophageal X-ray examination, May 15, the condition was exactly the same at the previous X-ray examination (Fig 1) Because of the shortage of beds the patient was put on the waiting list for operation She was feeling moderately well but relapses of dysphagia occurred from time to time In the autumn of 1961 the patient became pregnant and the difficulty in swallowing immediately increased Hypochromic anæmia developed

Fig 1 Oesophageal rœntgen studies showing achalasia with marked dilatation of the entire œsophagus May 15 1961



It was considered that therapeutic abortion was indicated and this was performed at the second month At the same time the patient was given contraceptive advice Dysphagia decreased considerably after termination of pregnancy

In the winter 1962 the patient became pregnant again, the last menstrual period being on Feb 26, 1962 Dysphagia at once began to increase and attacks of vomiting occurred In May 1962 she was admitted for evaluation Her general condition was good but she was pale Her weight was 57 kilograms and height 161 cm Moderate hypochromic anæmia was diagnosed hæmoglobin 9 2 gm %, red blood count 4 80 mill, serum iron 26 γ% Vomiting did not occur whilst she was in hospital The patient was able to take solid food and iron therapy by mouth started for correction of anæmia Termination of pregnancy was not considered necessary The patient was readmitted after one month because of increased discomfort Her general condition was still good and her weight had remained unchanged The hæmoglobin value was 9 9 gm%, the red blood count 4 4 mill The uterine fundus was four fingerbreadths above the symphysis In hospital vomiting ceased within two days, and the patient could eat almost any food The impression was that psychogenic factors played an important part, since the symptoms always lessened in hospital and it was known that the pregnancy was not desired The patient was discharged on July 5, 1962, and told to present herself for review at frequent intervals

The patient was next admitted on Sept. 13 1962 In spite of increased difficulty in deglutition she had not sought medical aid in the meantime She now felt that even liquid food stuck in the œsophagus Regurgitation seemed to be worse in the recumbent position The patient appeared fatigued She had lost 3 kilograms in weight in two months The blood pressure was 150/90 mm Hg There was no proteinuria but the sediment contained numerous leukocytes and large quantities of bacteria The hæmoglobin level was 10 7 gm%, the red blood count 3 5 mill Serum electrolytes were within normal limits serum protein 6 7 % Considering that she was already 7 months pregnant it was decided to try management by conservative methods until the fœtus was viable On œsophagoscopy Sept. 25 the œsophagus was found to be very much enlarged and filled with food remnants The mucosa was reddened and hæmorrhagic. Cardial bougienage was performed at intervals of a few days Repeated œsophagoscopic examinations showed no improvement in the con

dition of the œsophagus Weight remained unchanged and the patient did not improve subjectively during treatment

On Oct 10 irregular uterine contractions began and the patient was there fore transferred to the obstetric ward The fundus uteri was one finger-breadth above the umbilicus Fœtal heart sounds were normal rate 140/min The breech presented and the cervix was almost completely effated As it was evident that continuance of pregnancy would involve too great risks for the patient labour was induced on Oct 12 by artificial rupture of the fœtal membranes in spite of the breech presentation. It was assumed that the fœtus would not be viable and it did in fact die during delivery The patient was delivered of a still born boy weighing 1500 grams and 41 cm in length She stated that she wanted no more children. Since it was probable that subse quent pregnancies would also be associated with complications tubal steriliza tion was performed on Oct 15 The patient recovered uneventfully from this operation.

The dysphagia did not decrease much after delivery In November 1962 the patient was subjected to cardio-œsophageal myotomy by the method of Heller Recovery was normal Postoperative X ray examination showed normal passage of opaque mixture through the cardia The patient s subjective symptoms disappeared and she has been in excellent health since

Discussion

The ætiology of achalasia is still unknown Alnor (1959) assumes on the basis of experimental observations that this con- dition is largely due to impaired circulation in the cardial region As a result of this the neural elements of the cardia are destroyed, which in turn causes the clinical picture of achalasia to arise Terracol (1958) considers that achalasia is not a sharply defined disease but rather a syndrome due to various factors The ultimate result is disturbance in the innervation of the œsophagus

It is in most cases impossible to determine the moment of onset The œsophagus may already be considerably dilated when the disease i diagnosed The latent period may be fairly long The initial symptom is a sensation of slowing of the passage of food from œsophagus to the stomach At the same time a dull pain may be felt beneath the sternum Difficulties in swallowing usually in crease gradually, but sometimes symptoms develop acutely due for instance, to some emotional disturbance Some patients suffer from severe pain which is attributed to œsophagospasm This often occurs after meals

With the progress of the disease the most typical symptom of achalasia–regurgitation sets in It first occurs daily, but as the œsophagus enlarges diffusely it may appear for instance only every three days It is frequently observed that the patient cannot assume a recumbent position because of spillage of œsophageal contents into the trachea Secretion of mucus in the œsophagus may be so profuse that the patient may regurgitate mucus alone

The patient's general condition depends on the severity of the lesion If there is much regurgitation, the general condition may become very bad Slight difficulty in swallowing usually has no major effect on the general condition the patient can lead a normal life In severe cases aspirated material may cause serious complications Oesophageal contents are most often aspirated during sleep This may result in bronchopneumonia, lung abscess or bronchiectasis It has occasionally caused suffocation

Rœntgenologic study alone usually establishes the diagnosis If the œsophagus is diffusely dilated a mass may be visualized in the area of the mediastinum even in the absence of opaque medium A barium meal usually collects at the lower end of the œsophagus, giving rise to a fusiform shadow above the level of the diaphragm Using a large quantity of opaque mixture, the outline of the upper portion of the œsophagus also becomes visible

Only hypotheses can be put forward as regards the part played by pregnancy in the production or aggravation of achalasia Alnor thinks that even the angle at which the œsophagus opens into the stomach is of importance in the opening and closure of the cardia Thus it might be assumed that the elevation of the diaphragm occurring towards the end of pregnancy might be a factor in achalasia Rennie *et al* suppose that, in the 5 cases of short œsophagus described by them, the increase in intra abdominal pressure during pregnancy had influenced the onset of symptoms According to them, the increase in pressure caused reflux of gastric juice into the œsophagus During the first trimester of pregnancy the intra-abdominal pressure scarcely increases Scott and Deutsch consider that, in their patients with œsophagitis the main ætiological factor was gastro œsophageal reflux This reflux they attributed to relaxation of the cardio-œsophageal spincter during pregnancy In their opinion pregnancy vomiting also played

a considerable part in the production of œsophagitis It is possible that factors like these are of importance also in the aggravation of symptoms of achalasia in pregnancy Roques assumed that pregnancy may interfere with the act of swallowing, either by local irritation due to nausea or vomiting or by toxic action on the nerve endings In addition he thinks that pregnancy may induce a neurosis, which then leads to achalasia In fact it has often been noted that patients with this disease show pronounced neurotic features At times the disease starts after some emotional upheaval On the other hand, the disease may also be causative of the neurotic symptoms In the case presented here, pregnancy was not desired, and so psychogenic factors might have been responsible for increased symptoms during pregnancy Lindert also thinks that in his case neurotic and psychogenic influences played an important part

In all the cases dealt with above the symptoms of achalasia increased rapidly during pregnancy and this complicated pregnancy to a serious degree Achalasia has a general tendency to progression Even a slight aggravation can be expected to interfere with the wellbeing of the patient because of the increased need for nourishment during pregnancy Termination of pregnancy does not necessarily mean an improvement in the patient s condition it may remain permanently poor as in Lindert s case and the case here presented The possibility of gastrointestinal disease should be kept in mind when a pregnant patient complains of gastrointestinal distress and there is nausea and vomiting This is well exemplified by the observations of McCall *et al* (1961) They performed œsophagoscopy on 11 pregnant women with gastrointestinal pain Oesophagitis was diagnosed in all these cases

The treatment of achalasia clearly requires much more active procedures during pregnancy than ordinarily, since rapid deterioration threatens in pregnant patients Gastrostomy and digital dilatation of the cardia was performed on one of the two patients reported by Roques The patient, however, succumbed 12 hours after operation The other patient underwent the same operation after termination of pregnancy at the 5th month a good result was obtained Lindert s patient was subjected to cardiomyotomy by the method of Heller four months after delivery, with success In the case described by Stroup, operation was not necessary

With the progress of the disease the most typical symptom of achalasia–regurgitation sets in It first occurs daily, but as the œsophagus enlarges diffusely it may appear for instance only every three days It is frequently observated that the patient cannot assume a recumbent position because of spillage of œsophageal contents into the trachea Secretion of mucus in the œsophagus may be so profuse that the patient may regurgitate mucus alone

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Addendum

Since this paper was written the following article on the subject discussed has been published

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dilatation alone sufficed Roques says that pregnancy should first be terminated and surgical treatment of achalasia only then considered With present-day surgical and anæsthesiological methods, operation can obviously be done also during pregnancy, at least during the early stages In the present case the patient's condition had deteriorated to the extent that operation during pregnancy seemed too hazardous

SUMMARY

A severe case of achalasia associated with pregnancy is reported This combination has hitherto been described only a few times Achalasia can with good reason be considered a grave complication of pregnancy since it tends to be aggravated rapidly and results in deterioration of the patient's condition It is concluded that gastrointestinal distress in pregnant women requires careful studies with a view to early determination of the exact nature of the disease and its effect on the course of pregnancy

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diseases on clinical examination The systolic blood pressure was in every case below 125 mm of mercury

The non pregnant women selected were completely healthy nurses from the hospital, with regular menstrual cycles Four were in the luteal phase of the cycle (cases contr 1–4 in Tables I and III) and three in the postmenstrual phase (cases contr 5–7) of the menstrual cycle at the time of the experiment Their ages ranged between 19 and 28 years Pregnant and non pregnant women were subjected to the same experimental conditions

Before the day of the experiment the subject was fasted for 12 hours but was allowed to drink *ad libitum*. One and a half hours before the start she drank 0 5 to 1 litre of water The experiment was started at 7 30 a m with an intravenous drip infusion of 5 per cent dextrose solution The urine was collected during two successive 20 min periods by urethral catheter The excretion of sodium and potassium in μEq/min was estimated during each of the two periods and the average values were used as basal values for the test The creatinine clearance was determined during the same periods The dextrose infusion was followed by an angiotensin infusion using 0 5 mg synthetic Val Hypertensin II Asp-β amide (Ciba AG Basle) diluted in 1000 ml of 5 per cent dextrose solution The rate of drip to raise systolic and diastolic pressures by 20–30 mm of mercury above the initial values Blood pressure measurements were taken at 5 min intervals The angiotensin infusion phase lasted 20 min during which the urine volume was measured and sodium potassium and creatinine clearance determined as before The infusion of glucose was resumed immediately thereafter using the same drip rate as for angiotensin and the urine was collected and analyzed during the two subsequent 20 min periods Sodium, potassium and creatinine contents of urine and plasma were determined as reported earlier (Eisalo *et al* 1964) After the first angiotensin test each patient was given an intravenous infusion of the fat emulsion Infonutrol (Astra AB Sweden) for a period of 6 hours This infusion of Infonutrol was followed by a second angiotensin test which was carried out in exactly the same manner as the first

A statistical analysis was made of the changes observed in the relative excretion values for the individuals since the absolute changes may depend on the initial values Analysis and testing were used to examine the probability with which the logarithmic mean of the relative values is 0

Results

The vasopressor response

The amount of angiotensin required to raise the systolic blood pressure by 20 mm of mercury was measured There was no

Luukkainen T Eisalo A Järvinen P A and Viranko M Acta obst et gynec scandinav 43, [illegible] 1964

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EFFECT OF ANGIOTENSIN ON URINARY ELECTROLYTES BEFORE AND AFTER LIPID INFUSION IN EARLY HUMAN PREGNANCY

BY

TAPANI LUUKKAINEN ANTTI EISALO PENTTI A JÄRVINEN AND MATTI VIRANKO

It has been demonstrated that a lipid infusion, Infonutrol,[1] is effective in producing uterine activity in women in early pregnancy and at term (Järvinen *et al* 1963 Luukkainen *et al* 1964) Because large doses of this lipid infusion in rabbits (Luukkainen and Csapo, 1963) sometimes resulted in intrauterine death, the study was extended to investigate any possible effects of the lipid infusion on the human pregnant organism other than activation of the myometrium

The present investigation was undertaken to determine the vasopressor response of a normally present pressor substance, *viz* angiotensin, and its effect on urinary electrolytes, in volunteer pregnant and non pregnant women before and after infusion of Infonutrol

Methods

The eight pregnant women in the series were admitted to this hospital for legal abortion on psychiatric or sociological grounds Their ages were between 26 and 33 years and the stage of pregnancy ranged from 9 to 15 weeks None had any history of cardiovascular or renal disease or showed any signs of these

[1] Astra AB, Sweden

and of creatinine clearance values ($P < 0.05$) The potassium excretion was decreased in most of the cases, but the change was not statistically significant In the control group three out of the seven cases showed an elevation in the sodium and potassium excretion, which was accompanied by an increased creatinine clearance The other women showed a decrease in the electrolyte excretion and creatinine clearance Thus the changes during the first angiotensin infusion were not statistically significant

The second angiotensin infusion, which was given after the Infonutrol treatment, clearly decreased the sodium ($P < 0.001$) and potassium ($P < 0.01$) excretion and the creatinine clearance ($P < 0.01$) in the pregnant women

When the two angiotensin infusions were compared statistically as regards effectiveness it was observed that in the pregnant group the decrease in sodium and potassium excretion was statistically more pronounced ($P < 0.05$) during the second angiotensin infusion The creatinine clearance values were also lower during the second infusion than during the first, but the decrease was not significant ($P \sim 0.06$)

In the control group, during the second angiotensin infusion, given after the Infonutrol infusion, the electrolyte excretion and creatinine clearance were usually lower than during the preceding dextrose infusion periods This change was not statistically significant

The statistical comparison of the effects on the electrolyte excretion and creatinine clearance values observed during the first and second angiotensin infusions revealed no significant change in the effectiveness of the angiotensin in the control group However this group consisted of two subgroups in different phases of the menstrual period The women in the luteal phase (control cases 1–4) showed a smaller response during the second angiotensin infusion than during the first one in every parameter studied But in the women who were in the postmenstrual phase of their cycle (cases 6–7), the second infusion produced a more pronounced decrease in the electrolyte excretion and the creatinine clearance than the first infusion

The urinary electrolyte and creatinine clearance values deter-

significant difference between the first and second angiotensin tests in the pregnant group or between the pregnant and non-pregnant groups The dose of angiotensin required to produce this rise varied with the individual from 1 0 to 1 6 μg/min

Urinary electrolytes and creatinine clearance values

The percentage changes in the excretion of electrolytes and in the creatinine clearance values due to the first angiotensin infusion and to the second, made after the lipid infusion, are given in Table I

In pregnant women the first angiotensin infusion resulted in a statistically significant decrease of sodium excretion ($P < 0\ 05$)

Table I *Effect of Angiotensin Infusion before and after Infonutrol on Urinary Electrolyte Excretion and Creatinine Clearance*

Sodium and potassium were determined in μEq/min creatinine clearance ml/min Basal values are the mean of two successive measurements during a dextrose infusion preceding each angiotensin infusion 1st A = first angiotensin infusion 2nd A = second angiotensin infusion given after an Infonutrol infusion of 500 ml Preg = pregnant women Cont = non pregnant controls

	Percentage Change from Basal Values					
Group	Sodium		Potassium		Creatinine clearance	
	1st A	2nd A	1st A	2nd A	1st A	2nd A
Preg 1	−59	−70	−21	−60	−33	−55
Preg 2	−38	−67	−30	−74	−28	−64
Preg 3	+72	−57	+48	− 9	− 3	−84
Preg 4	−34	−81	+ 8	−68	− 8	−50
Preg 5	−49	−82	−17	−84	−20	−70
Preg 6	−52	−45	−34	−41	−25	−43
Preg 7	−30	−22	− 2	−16	−37	−
Preg 8	−68	−77	−54	−54	−53	−40
Mean	−32 2	−62 6	−12 7	−46 7	−23 1	−53 2
Cont 1	−72	−25	−35	−10	−44	−21
Cont 2	−72	+24	−31	+46	−24	53
Cont 3	−89	−32	−71	− 9	−50	−13
Cont 4	+27	−37	−26	−34	− 9	11
Cont 5	+42	−80	−69	−73	54	−40
Cont 6	+99	−52	−85	−50	−81	−53
Cont 7	−42	−72	−38	−65	−26	−52
Mean	−15 2	−29 9	− 0 7	−18 1	− 3 7	−13 5

and of creatinine clearance values ($P < 0\,05$) The potassium excretion was decreased in most of the cases, but the change was not statistically significant In the control group three out of the seven cases showed an elevation in the sodium and potassium excretion, which was accompanied by an increased creatinine clearance The other women showed a decrease in the electrolyte excretion and creatinine clearance Thus the changes during the first angiotensin infusion were not statistically significant

The second angiotensin infusion, which was given after the Infonutrol treatment, clearly decreased the sodium ($P < 0\,001$) and potassium ($P < 0\,01$) excretion and the creatinine clearance ($P < 0\,01$) in the pregnant women

When the two angiotensin infusions were compared statistically as regards effectiveness it was observed that in the pregnant group the decrease in sodium and potassium excretion was statistically more pronounced ($P < 0\,05$) during the second angiotensin infusion The creatinine clearance values were also lower during the second infusion than during the first, but the decrease was not significant ($P \sim 0\,06$)

In the control group, during the second angiotensin infusion, given after the Infonutrol infusion, the electrolyte excretion and creatinine clearance were usually lower than during the preceding dextrose infusion periods This change was not statistically significant

The statistical comparison of the effects on the electrolyte excretion and creatinine clearance values observed during the first and second angiotensin infusions revealed no significant change in the effectiveness of the angiotensin in the control group However this group consisted of two subgroups in different phases of the menstrual period The women in the luteal phase (control cases 1–4) showed a smaller response during the second angiotensin infusion than during the first one in every parameter studied But in the women who were in the postmenstrual phase of their cycle (cases 6–7) the second infusion produced a more pronounced decrease in the electrolyte excretion and the creatinine clearance than the first infusion

The urinary electrolyte and creatinine clearance values deter-

Table II *The Effect of Infonutrol Infusion on Urinary Electrolyte Excretion and Creatinine Clearance Values*

Electrolytes μEq/min creatinine clearance ml/min B I = Before Infonutrol A I = after Infonutrol % = calculated percentage change Preg = pregnant women *Cont = non pregnant controls*

Case	Sodium			Potassium			Creatinine Clearance		
	B I	A I	%	B I	A I	%	B I	A I	%
Preg 1	197	98	−50	66	53	−20	1 6	93	− 6
Preg 2	206	148	−22	69	47	−32	85	117	+ 37
Preg 3	65	21	−68	31	33	+ 6	50	100	+100
Preg 4	124	172	+40	40	66	+65	60	114	+ 90
Preg 5	176	191	+ 8	73	31	−58	84	91	+ 8
Preg 6	307	71	− 6	119	73	−39	97	88	− 9
Preg 7	187	176	− 6	95	49	−48	165	122	− 16
Preg 8	185	161	−13	110	50	−55	86	131	+ 52
Mean			−23 4			−22 6			+ 9 5
Cont 1	175	60	−66	100	20	−80	155	81	− 48
Cont 2	160	42	−74	78	26	−67	128	106	− 17
Cont 3	120	213	+77	55	22	−60	86	70	− 19
Cont 4	436	389	−11	113	125	+ 10	74	83	+ 12
Cont 5	294	171	−42	45	2	−51	81	94	+ 16
Cont 6	120	59	−50	59	18	− 0	104	101	− 3
Cont 7	114	134	+17	52	85	+63	116	165	42
Mean			−21 3			−36 4			4

mined before and after the lipid infusion and the percentage changes in these values are given in Table II There seems to be a sodium and potassium retention effect in most patients in the pregnant as well as the non pregnant group The creatinine clearance was increased in five out of the eight patients in the pregnant group whereas in the non pregnant group the effect was irregular The effects observed after lipid infusion were not statistically significant

Discussion

The results of the present investigation suggest that in the experimental conditions used a phospholipid-containing fat emulsion Infonutrol produces an increased response to angiotensin infusion in women in the early stages of pregnancy which in

turn is manifested by increased retention of sodium and potassium and a decreased glomerular filtration rate as judged by the creatinine clearance values The lipid infusion as such has a small but statistically insignificant effect on sodium and potassium retention without decreasing the glomerular filtration rate

The non pregnant women who were in the luteal phase of their menstrual cycle seemed to show a smaller effect of angiotensin on the urinary electrolyte excretion during the second angiotensin infusion, given after Infonutrol treatment, than during the first infusion On the other hand, it was found that in all the non pregnant women in the postmenstrual phase the electrolyte excretion decreased more during the second angiotensin infusion than during the first one This difference between the two control groups appears more likely to be dependent on the different phases of the menstrual cycle than to be due purely to chance

The mode of action of the phospholipid infusion in modifying the electrolyte effect of angiotensin remains obscure and it is completely unknown whether or not human pregnant organisms contain a physiological compound which, like the model substance, Infonutrol can produce myometric contractions in early pregnancy (Järvinen *et al* 1963), induce delivery at term Luukkainen *et al* 1964), or as in the present investigation, modify the effect of angiotensin on urinary electrolyte excretion

It has been reported by Boyd (1936) that toxæmic symptoms are associated with elevated plasma phospholipids In a recent investigation, Alvarez and Bratvold (1961) were unable to confirm his results at a statistically significant level It seems, however that the fractionation of blood phospholipids in toxæmic patients would repay further investigation

SUMMARY

The effect of angiotensin infusion on urinary electrolyte excretion was studied before and after an intravenous infusion of a fat emulsion Infonutrol in eight women 9–15 weeks pregnant and in seven non pregnant women

In the pregnant group electrolyte retention was increased more during the angiotensin infusion given after the Infonutrol

infusion than during the angiotensin infusion given before the lipid treatment, and the difference was statistically significant

The four non-pregnant women who were in the luteal phase showed no increased effect of angiotensin on the electrolytes after the lipid infusion, whereas the three who were in the postmenstrual phase of the cycle showed a response similar to that of the pregnant women

Acknowledgements

We are grateful to the Sigrid Juselius Foundation for a grant and Astra AB of Sodertälje, Sweden, and Ciba AG of Basle, Switzerland, for generously supplying Infonutrol and Hypertensin

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BACTERIURIA IN PREGNANCY ITS FREQUENCY AND RELATION TO OVERT URINARY INFECTION

BY

ANDERS FORKMAN

Recent research has shown that acute urinary infection is not an isolated readily curable, phenomenon but rather a disease which unless properly treated, is liable to recur and lead to chronic renal disease

This more serious view of acute urinary tract infection has increased the importance of bacteriological analysis of the urine Evaluation of urine cultures is difficult owing to contaminating bacteria from the distal urethra and the urethral orifice (Bradley and Little, 1963, and others) Routine catheterization to avoid such contamination is undesirable because of the risk of infection associated with this procedure (Kass 1957 Brumfitt *et al*, 1961 Kaye *et al* 1962 Slotnick and Prystowsky, 1962) According to some investigators however reliable cultures can be obtained with clean voided samples (Kass, 1957 Monzon *et al* 1958 Jackson *et al*, 1958 Sachse *et al* 1961 Virtanen 1962) Kass (1957) stated that demonstration of more than 100 000 bact /ml urine in such a sample justifies a diagnosis of significant bacteriuria

These principles have since been applied in the quantitative culture of urine in large series of patients and the results have been correlated with sex age social group socio-economic level various diseases etc (Kass 1957 Merrit and Sanford, 1958 Kunin *et al* 1960 Mulla 1960 OSullivan 1961 Switzer, 1961 Lystad and Gardborg 1963, and others) Such investigations have revealed that clinical manifestations of urinary

infusion than during the angiotensin infusion given before the lipid treatment, and the difference was statistically significant

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50 patients who had 5 years previously had urinary tract infection during pregnancy Pinkerton *et al* (1961) reported recurrences of urinary tract infection in 80 per cent, in half of whom urographic abnormalities were also demonstrated

Since the investigations referred to above suggest that bacteriuria during pregnancy may result in protracted and serious late complications a random selection of the women attending an antenatal clinic (Lund) in 1961–1962 were studied for bacteriuria

Material and Methods

The series consisted of 595 pregnant women, who were followed up until 1 week after parturition During the pregnancy in question 11 of these women had been treated for overt urinary infection before the present investigation was started These women were not included in the calculation of the frequency of bacteriuria They were, however included in the calculation of the frequency of overt urinary infection in pregnancy

In order to secure a random selection samples were collected from the first 15 women seen at the antenatal clinic on each reception day Samples were often collected from the same woman on more than one occasion The women were instructed by the nurse to wash the vulva with a detergent before urination The samples were kept at +4° C until the daily number had been collected, after which they were sent to the bacteriological laboratory in a chilled vacuum container As a rule semi-quantitative culture (see below) and gram staining were done as soon as the samples arrived at the laboratory Samples not studied at once were stored at +4° C and cultured within 24 hours of collection As expected from the work of Ryan and Mills (1963), control tests of 200 urine samples showed that 24 hours storage at +4° C does not affect the result of culture The results of gram-staining of the urinary sediments will be reported separately elsewhere

The technique used for semi quantitative culture is illustrated diagrammatically in Fig 1 0 01 ml of the undiluted urine was removed with the aid of a standard platinum loop and spread

tract infections are often preceded by asymptomatic significant bacteriuria

Urinary tract infections are common in pregnancy One might therefore expect the frequency of bacteriuria to be increased during gestation The frequency of bacteriuria in pregnancy was studied by Kass (1959), in 4,000 women, the largest series on record He found a frequency of 6 per cent Of 200 unmarried, apparently healthy, female non-pregnant controls he found significant bacteriuria in 0 5 per cent Of particular interest was the further course in the pregnant women with bacteriuria When the bacteriuria was left untreated, clinical manifestations of urinary tract infection occurred in 40 per cent during the rest of pregnancy or the puerperium, but in none of the women in whom the condition was treated At follow-up 3 months after parturition three fourths of the untreated women still had significant bacteriuria Kass also found that 24 per cent of the deliveries in the group with untreated bacteriuria were premature, against 9 per cent in his control series

Further similar investigations of the frequency of bacteriuria in pregnancy have since been reported (Kaitz, 1960, Mulla, 1960, Turner, 1961, Virtanen, 1962, Chalmers, 1963 Monto and Rantz, 1963) Turner found significant bacteriuria in 7 per cent of 1,500 pregnant women, against 1 per cent of 200 young, unmarried non pregnant controls Of women with untreated bacteriuria, clinical manifestations of urinary tract infection occurred in 60 per cent Only 1 5 per cent of the women with less than 100,000 bact /ml urine showed symptoms In Turner s series the frequency of premature births did not vary with the presence or absence of maternal bacteriuria

Kaitz (1961) found the concentrating capacity of the kidneys to be significantly lower in pregnancies complicated by bacteriuria

Several investigations suggest that the later course or sequelae of an apparently transient urinary tract infection during pregnancy may sometimes be serious On careful after-examination of 77 patients admitted to hospital within a 15 year period because of active pyelonephritis of pregnancy, Kremling and Winckler (1962) found persistent pyelonephritis and renal insufficiency in as many as 25 per cent On after-examination of

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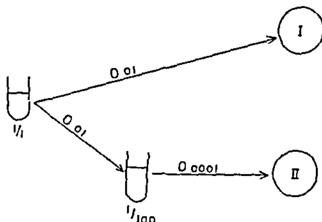


Fig 1 Diagram of semi-quantitative culture of urine Values denote concentration of urine in test tubes and volume (ml) transferred with platinum loop to dilution tube and plates

on a blood agar plate With the same loop the remaining urine was then diluted 1 100 with physiological saline and about 0 01 ml was spread on a second similar plate (Plate II) This procedure, which is a modification of Hoeprich s (1960), is simple and has proved reliable and has been used routinely since 1961 at the Institute of Bacteriology, Lund The method allows approximate estimation of the number of bacteria within a concentration range of 100 to 5 million bact /ml The plates were *incubated at 37° C for 18 hours* Conventional criteria were used in the classification of the bacteria

Results

Frequency of significant bacteriuria

The samples were grouped according to the number of bacteria per millilitre of urine (Fig 2) As in published investigations (Kass, 1955, Virtanen, 1962, Effersoe and Jensen, 1963) the majority of samples contained less than 10^4 bact /ml or more than 10^5 bact /ml (91 per cent and 6 per cent respectively) In the intermediate group, 10^4—10^5 bact /ml, 22 of the 24 samples

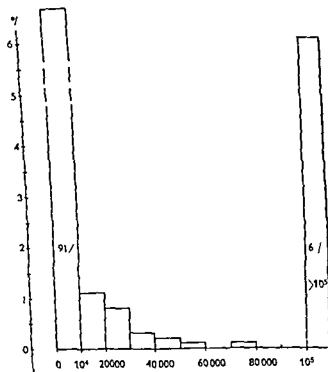


Fig 2 Frequency distribution of urine samples according to number of pathogenic bacteria per millilitre (E coli coliform Proteus and enterococci)

contained less than 50 000 bact/ml, a concentration closer to the group $< 10^4$ than the $> 10^5$ group Therefore as in Kass investigation, the border for significant bacteriuria was set at 10^5 bact/ml With this criterion, 34 (6 per cent) of 584 patients were found to have significant bacteriuria (Table I)

The bacteria that occurred in the groups with significant bacteriuria were *E coli* coliform bacteria *Proteus* and enterococci (Table II) Coagulase negative *Staphylococcus albus* was demonstrated in a concentration of $> 10^5$ bact./ml in samples from 10 women In 3 of these 10 women *Staphylococcus albus* was demonstrated repeatedly in the remaining 7 only on one occasion

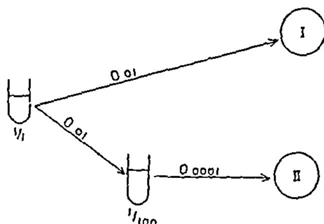


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nitrofurantoin (1 woman) In none of them did symptoms of urinary tract infection occur

Overt urinary infection occurred in 7 (24 per cent) of the 29 women in the group who had significant bacteriuria but who did not receive prophylaxis Of the 550 patients without significant bacteriuria symptoms of urinary tract infection developed in 21 (4 per cent) The difference in frequency was highly significant ($p < 0\ 001$)

Symptoms of urinary tract infection appeared during pregnancy in 3 women with and in 7 without previously known bacteriuria Such symptoms began in the puerperium in 4 patients with, and in 14 without, previously known bacteriuria (Table IV)

Sampling was started in 27 patients in the first, 170 in the second and 387 in the third trimester (Table V) Bacteriuria was demonstrated for the first time in none of the women in the first trimester, in 12 (7 per cent) in the second, and in 22 (6 per cent) in the third trimester All of the cases of bacteriuria were discovered in the trimester in which the first sample was studied, except in one patient in whom the urine was negative in the second and positive in the third trimester The frequency of bacteriuria in the second and third trimester did not differ significantly ($p > 0\ 2$) The number of patients in the first trimester was not large enough to warrant estimation of the frequency of bacteriuria at this early stage

Of the patients studied 303 were gravidæ I 181 were gravidæ II and 100 were multigravidæ (Table VI) Of the 34 women in whom asymptomatic significant bacteriuria was found, 15 were pregnant for the first time, 15 for the second and 4 were multigravidæ The difference between the frequency of asymptomatic bacteriuria in primigravidæ and multigravidæ was not statistically significant ($p > 0\ 2$)

Overt urinary infection in pregnancy and the puerperium

The occurrence of overt urinary infection during pregnancy and the puerperium was also studied irrespective of previously diagnosed bacteriuria

Symptoms of urinary tract infection occurred in 6 5 per cent

Table I *Frequency of Significant Bacteriuria among 584 Pregnant Women*

Bact./ml	Number of Patients
$>10^5$	34 (6%)
$<10^5$	550 (94%)

Table II *Types of Bacteria Isolated from Urine in 34 Pregnant Women with Asymptomatic Bacteriuria*

Types of Bacteria	Patients
E. coli, coliform	26
Proteus	1
Enterococci	6
Mixed flora	
Proteus + E. coli	1

Table III *Frequency of Symptoms of Urinary Tract Infection among Patients with Untreated Bacteriuria and without Significant Bacteriuria*

	$>10^5$ Bact./ml	$<10^5$ Bact./ml
Total number of untreated patients	29	550
Number with symptoms	7 (24%)	21 (4%)

None of these women developed symptoms of urinary tract infection. Since the finding of coagulase-negative *Staphylococcus albus* was considered irrelevant, these 10 cases were not regarded as having significant bacteriuria and were classified accordingly.

Asymptomatic bacteriuria—clinical urinary tract infection

Table III compares the frequency of overt urinary infection in patients with previously untreated significant bacteriuria and without known bacteriuria. The manifestations considered relevant were: burning pain on micturition, pain in the flanks, pyuria and fever. Only when the patient had at least two of these symptoms was she said to have overt urinary infection. Frequency of urination was not regarded as a specific symptom of urinary tract infection.

Five of the women in the group with significant bacteriuria were treated for 2 weeks with sulphonamides (4 women) or with

Table VIII *Frequency of Overt Urinary Infection in Relation to Number of Previous Pregnancies*

Number of Previous Pregnancies	Total Number of Patients	Number of Patients with Symptoms of Urinary Tract Infection
0	311	26
1	184	9
>1	100	4

of the 595 women (Table VII) The occurrence of such symptoms was roughly equal in the first and second trimesters and somewhat higher in the third (1 7 per cent and 3 0 per cent respectively)

The relation between parity and overt urinary infection is given in Table VIII from which it is seen that such infections were noted in 26 (8 per cent) of the 311 primigravidæ, against 13 (5 per cent) of the 284 multigravidæ The difference was not statistically significant ($p > 0\ 05$)

The patients with overt urinary infection received sulphonamidetherapy for 14 days In all of the 21 women treated in this way the symptoms soon disappeared, but in 3 of them symptoms recurred during the puerperium

Prematurity

Twenty (3 4 per cent) of the 595 mothers delivered prematurely (birthweight < 2,500 gr) Only one (2 9 per cent) of the 34 mothers with diagnosed asymptomatic bacteriuria delivered a premature infant She had not received sulphonamidetherapy Nor had she had any symptoms of urinary tract infection Of all the 2 707 children born at the department of obstetrics Lund University Hospital in 1962 4 8 per cent were premature

Discussion

The investigation method presupposes that culture of the samples allows definite and reliable distinction between contaminated and primarily infected urine In studies using this method significant bacteriuria is usually said to be present if the samples contains more than 10^5 bact./ml all concentrations below this limit being ascribed to contamination (Kass, 1955

Table IV Frequency of Symptoms of Urinary Tract Infection among Patients with Treated and Untreated Bacteriuria and Patients without Significant Bacteriuria

	Number of Patients with Bacteriuria		Number of Patients without Bacteriuria
	Treated	Untreated	
Symptoms appearing during pregnancy	0	3	7
Symptoms appearing in puerperium	0	4	24
No symptoms	5	22	520
Total number of patients	5	29	550

Table V *Frequency of Significant Bacteriuria Grouped According to Stage of Pregnancy at Time of First Culture*

Trimester	Total Number of Patients	Number of Patients with Significant Bacteriuria
I	27	0
II	170	12
III	387	22

Table VI *Frequency of Significant Bacteriuria in Relation to Number of Previous Pregnancies*

Number of Previous Pregnancies	Total Number of Patients	Number of Patients with Significant Bacteriuria
0	303	15
1	181	15
>1	100	4

Table VII *Stage of Pregnancy at Onset of Symptoms of Urinary Tract Infection*

	Number of Patients
Trimester I	1
Trimester II	10
Trimester III	10
Puerperium	18
Total	39 (6.5 % of 595)

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Sanford, 1959, Turner, 1961, Virtanen, 1962) Some authors have suggested a lower limit, namely 10^4 bact./ml (Effersoe and Jensen, 1963) or 10^3 bact./ml (Sanford *et al*, 1956)

In the present investigation nearly all of the few samples that contained 10^4—10^5 bact./ml had 10,000—50,000 bact./ml and were closer to the large group of contaminated samples with $< 10^4$ bact./ml None of the samples fell within the neighbourhood of 10^5 bact./ml (Fig 2) Therefore 10^5 bact./ml was taken as the limit Such a limit, however, presupposes that the samples are kept and transported at refrigerator temperature (about +4° C)

The limit given for significant bacteriuria is reliable for untreated patients, such as in the present series of pregnant women But it does not hold for patients undergoing antibacterial treatment

Significant bacteriuria was found in 6 per cent of the pregnant women Several previous investigators have found frequencies of 0 5—1 per cent bacteriuria in young unmarried non pregnant women (Kass, 1960, Turner, 1961, Chalmers, 1963) In addition Chalmers (1963) found bacteriuria in 5—6 per cent of married nulligravidæ in Aberdeen, against 6 8 per cent in pregnant women It has thus not been shown with certainty that bacteriuria is more common in pregnancy Chalmers findings suggest sexual intercourse to be an ætiological factor in this respect

The results clearly show that further investigations are desirable to ascertain what requirements a control series should satisfy to be regarded as acceptable Such investigations and control series will be the subject of a future paper

The frequency (24 per cent) of symptoms of urinary tract infection in pregnant women with untreated bacteriuria in the present investigation was lower than that found by other investigators (40—60 per cent) But in published series the clinical criteria of urinary tract infection are not specified and may therefore be less stringent

The high frequency of overt urinary infection in pregnant women with untreated bacteriuria compared with that in pregnant

women without bacteriuria or with treated bacteriuria is striking. This appears to be the most important finding in the investigation, since it suggests the possibility of reducing the frequency of overt urinary infection during pregnancy and the puerperium.

It cannot be stated with certainty that pregnancy complicated by asymptomatic bacteriuria is associated with symptoms of urinary tract infection more often than other conditions associated with asymptomatic bacteriuria. In a survey of 309 consecutive admissions to a medical and a surgical ward service Kass (1960) found 53 patients with significant bacteriuria. In 75 per cent the condition was asymptomatic. During their stay in hospital symptoms of urinary tract infection developed in one third of the patients who had bacteriuria at the time of admission but in none of those without significant bacteriuria at the time of admission.

Of the factors of possible ætiological importance in bacteriuria and urinary tract infection in pregnancy most attention has been given to the anatomical changes of the urinary tract during pregnancy (Beeson 1955). This applies to dilatation of the renal pelvis and ureters, which favours the development of urinary stasis. It was therefore thought worth while to find out when in pregnancy bacteriuria or symptoms of urinary tract infection tended to appear. Kass (1960) found that bacteriuria occurred initially in the second month of pregnancy in about 5 per cent of all women and that this frequency persisted unchanged throughout the rest of pregnancy despite the increasing anatomical changes.

The frequency of bacteriuria in the first trimester could not be judged in the present material because of the small number of women examined at this early stage. No statistically significant difference regarding the frequency of bacteriuria was found between the second and third trimester. The fact that the frequency of bacteriuria did not increase during the latter part of pregnancy suggests that factors other than the anatomical changes may also be of ætiological importance.

Two thirds of the cases of clinically manifest infections occurred after parturition. It is possible that quantitative urine culture just before parturition could have revealed bacteriuria in some of these patients who could then have received early treatment

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The high frequency of overt urinary infection in pregnant women with untreated bacteriuria compared with that in pregnant

before parturition Cessation of treatment should therefore be followed by repeated bacteriological examination of the urine throughout the rest of pregnancy and especially just before parturition

It has been questioned whether the advantages of such a procedure are not more than outweighed by the disadvantages involved increased work load, increased risk of drug allergy increased resistance of the bacteria etc (Obstetrical and Gynecological Survey, 1962 a, b idem, 1963) Several of the investigations referred to above suggest the possibility of correlation between asymptomatic bacteriuria overt urinary infection, and chronic pyelonephritis This alone is surely sufficient to warrant prophylaxis in patients with known significant bacteriuria during pregnancy Compared with the risk of chronic pyelonephritis the above mentioned disadvantages of such treatment are negligible

SUMMARY

Urine samples from 595 pregnant women were examined by a simplified method of quantitative culture Significant bacteriuria was noted in 6 per cent Of pregnant women with untreated asymptomatic bacteriuria overt urinary infection appeared later during pregnancy or in the puerperium in 24 per cent The corresponding number for pregnant women without significant bacteriuria was 4 per cent

Of the clinically manifest cases of urinary tract infection, two thirds appeared in the puerperium Negative cultures did not exclude the possibility of bacteriuria and overt urinary infection later during pregnancy or in the puerperium

The results of the investigation underline the necessity for repeated bacteriological examination of the urine during pregnancy and especially just before parturition

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Turck and Petersdorf (1962) has shown a correlation between asymptomatic bacteriuria immediately before delivery and manifest clinical infection during the puerperium

In this connection it might be mentioned that in our hospital the urinary bladder is not routinely catheterized in association with parturition When catheterisation is necessary, it is always combined with insertion of an antiseptic (mercurochrome) in the urinary bladder, a procedure that has been described as providing good prophylaxis (Paterson et al, 1960)

No correlation was found in the present investigation between maternal bacteriuria and premature delivery Kass (1959) and Henderson et al (1959) found such a correlation while Turner (1961) and Chalmers (1963) were not able to demonstrate any such correlation Henderson et al found a high frequency of bacteriuria as well as of prematurity in patients belonging to the low socio economic class Henderson et al however, did not believe in any causal relationship between bacteriuria and prematurity

In the present investigation the bacterial flora consisted mainly, and sometimes entirely, of bacteria belonging to the coli group These bacteria were invariable susceptible to sulphonamides

The investigation showed that asymptomatic bacteriuria in pregnancy can, if left untreated, have serious consequences It also showed that clinical urinary tract infection may occur in women in whom culture of urine collected on one or more occasions during pregnancy has not shown significant bacteriuria

If overt urinary infection is to be prevented, the urine should be studied for bacteria at regular intervals during pregnancy Such a procedure would be useful but would overburden the antenatal clinics and the bacteriological laboratories In view of the relatively high frequency of urinary tract infections in the puerperium, however, the urine should be examined bacteriologically just before parturition Such an examination could be introduced as a routine procedure and would not involve any substantial extra burden on departments of obstetrics or bacteriology

It has been shown (Kass, 1959) that if treatment of bacteriuria is stopped during pregnancy the bacteriuria will usually recur

Bengtsson, Lars Ph and Ejarque Peter M Acta obst. et gynec. scandinav 43, 49 1964.

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PRODUCTION RATE OF PROGESTERONE IN THE LAST MONTH OF HUMAN PREGNANCY

BY

LARS PH BENGTSSON AND PETER M. EJARQUE

The significance of progesterone in the maintenance of human pregnancy has been under discussion for several decades Until recently most research in progesterone problems in the human was performed by means of urinary pregnanediol determinations in normal and abnormal pregnancies and by therapeutic trials of gestagens in threatened abortion and premature labour It is now evident that these complicated problems must be attacked on a much broader basis including the chemistry, production, circulation storage metabolism, excretion and physiology of progesterone

One of the first links in this chain of problems is the rate of progesterone production in different stages of pregnancy This is of both theoretical and clinical significance From a theoretical point of view it should be known whether the reactivity of the myometrium during human pregnancy is related to the amount of progesterone produced as it seems to be in the rabbit (Mikhail *et al*, 1961) From a clinical point of view only reliable data on the rate of progesterone production in normal pregnancy can guide our attempts to compensate for a suspected progesterone insufficiency

Considerable technical difficulties however, are involved in determination of the rate of progesterone production in human pregnancy So far there is only one report on progesterone production in midpregnancy (Ejarque and Bengtsson 1962) and

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was adapted for our experimental conditions in

$$D = \frac{0\ 78\ \ S\ \ W}{C\ \ d}$$

where D is the dilution factor in mg/12 hr

0 78 is the ratio between molecular weights of progesterone and pregnanediol diacetate

S is the specific activity of the progesterone 4 ^{14}C (83 05 μc/mg)

W is the amount of progesterone 4 ^{14}C injected in mg

C is the cumulative specific activity of pregnanediol diacetate in μc/mg

d is the number of urine collections (12 hr samples)

The cumulative specific activity of a urinary metabolite in a particular time may be obtained by determining the specific activ ity of the metabolite isolated from the urine pooled in that time, or may be calculated as in our experiments, by the cumulative aver aging of the specific activities of the metabolite isolated from the urine collected in fractions of that time The validity of the equa- tion in our experiments is discussed elsewhere (Ejarque and Bengtsson 1962)

Table I *Dilution factor estimation of progesterone 4 ^{14} C administered i v 30 days before term based on the specific activity determination of urinary preg nanediol diacetate isolated from 12 hr samples*

D y	Pr gnaned ol D ac tate Isolated		Cumulative Specific Act ity µc mg	Dilution Factor mg 12 hr
	Crystals mg	Specific Activity Dpt mg		
1 2	11 4	57 00	0 00154054	125 30
1	12 5	7 97	0 00087797	109 93
1 1 2	11 3	4 31	0 00062414	103 09
2	13 9	2 85	0 00048736	99 02
2 1/2	16 8	2 11	0 00040129	96 20
3	16 7	1 69	0 00034202	94 06
3 1 2	16 1	1 13	0 00029752	92 68
4	7 1	1 00	0 00026371	91 50

only some few on progesterone production in late pregnancy using the isotope dilution technique Pearlman (1957) and Solomon et al (1962) found a progesterone production of about 250 mg/day Similar results were obtained by Zander (1955, 1959) on the basis of the progesterone concentration in uterine vein blood and uterine blood flow

The present experiments represent a continuation of the earlier work on the production rate of progesterone in midpregnancy (Ejarque and Bengtsson, 1962) and were performed using the same technique

Experimental

Progesterone-4-^{14}C (Radiochemical Centre, Amersham, Buckinghamshire, England, reported activity 83 0 μc/mg) was purified by paper chromatography in a ligroin/propylene glycol system and found to have a specific activity of 83 05 μc/mg The radioactive progesterone was dissolved in ethanol Aliquots ready for injection were prepared in test tubes and kept in the cool Before injection physiological saline was added to make a 50 % solution In order to calculate the net amount of injected progesterone 4 ^{14}C, the needles, syringes and tubes used for the i v injection were extracted with large amounts of alcohol and an aliquot assayed for radioactivity Four pregnant women in their 36th, 38th, 39th, and 40th week of pregnancy (counted retrospectively from the day of spontaneous delivery) were injected with 2 92 (0 2431 μc), 2 98 (0 2479 μc), 2 96 (0 2453 μc) and 2 94 μg (0 2445 μc) of progesterone-4-^{14}C respectively A fifth woman in her 39th week of twin pregnancy received 2 95 μg (0 2456 μc) of progesterone 4-^{14}C The urine was collected in 12 hr samples and the specific activity of isolated pregnanediol diacetate was determined as described elsewhere (Ejarque and Bengtsson, 1962)

Results

The equation ordinarily used for the isotope dilution method

$$\text{secretory rate} = \frac{\text{radioactivity injected}}{\text{cumulative specific activity of urinary metabolite} \quad \text{time}}$$

Table IV Dilution factor estimation of progesterone 4 ^{14}C administered i v 2 1/2 days before term based on the specific activity determination of urinary pregnanediol diacetate isolated from 12 hr samples

Day	Pregnanediol Diacetate Isolated		Cumulative Specific Activity µc mg	Dilution Factor mg 12 hr
	Crystals mg	Specific Activity Dps mg		
1/2	10 8	47 12	0 00127351	149 54
1	7 6	12 32	0 00080324	118 55
1 1/2	8 1	6 45	0 00059360	106 94
1 2/3	1 2	5 04	0 00047925	108 39

For technical reasons only a 4 hr collection was obtained

Table V Dilution factor estimation of progesterone 4 ^{14}C administered i v in a twin pregnancy 7 days before term based on the specific activity determination of urinary pregnanediol diacetate isolated from 12 hr samples

Day	Pregnanediol Diacet te Isolated		Cumulative Specific Activity µc mg	Dilution Factor mg/12 hr
	Crystals mg	Specific Activity Dps mg		
1 2	17 0	16 07	0 00043432	439 99
1	16 9	6 23	0 00030134	317 07
1 1/2	10 0	1 99	0 00021882	291 09
2	7 4	1 43	0 00017377	274 01
2 1/2	18 2	0 59	0 00014221	268 75
3	9 1	0 41	0 00012035	264 63
3 1/2	6 4	0 27	0 00010420	261 82
4	7 8	0 16	0 00009171	260 28

of the urine collections in the five cases The dilution factor of the first 12 hr urine colection represents the totalt amount of steroid involved in the dilution expressed as an average obtained after 12 hr of dilution The steroid participating in the first dilution is

a) steroid stored in the tissues, and

b) steroid produced during the collection period

The dilution factor of the last urine collection represents the secretion rate of progesterone in mg/12 hr (as the processes have

Table II Dilution factor estimation of progesterone-4 ^{14}C administered i v 15 days before term based on the specific activity determination of urinary preg nanediol diacetate isolated from 12 hr samples

Day	Pregnanediol Diacetate Isolated		Cumulative Specific Activity μc mg	Dilution Factor mg 12 hr
	Crystals mg	Specific Activity Dps/mg		
1/2	11 5	38 25	0 00103378	185 48
1	5 3	5 55	0 00059189	161 97
1 1/2	7 2	2 23	0 00041468	154 13
2	10 9	1.49	0 00032108	149 29
2 1/2	4 5	0 43	0 00025918	147 96
3	13 2	0 29	0 00021728	147 08
3 1/2	3 4	0 12	0 00018670	146 71
4	12 0	0 10	0 00016370	146 41

Table III *Dilution factor estimation of progesterone-4* ^{14}C *administered i v 7 days before term based on the specific activity determination of urinary preg nanediol diacetate isolated from 12 hr samples*

Day	Pregnanediol Diacetate Isolated		Cumulative Specific Activity μc mg	Dilution Factor mg 12 hr
	Crystals mg	Specific Activity Dps mg		
1/2	21 1	28 52	0 00077081	245 39
1	25 9	5 30	0 00045202	206 94
1 1/2	21 7	2 33	0 00032567	193 60
2	31 5	1 24	0 00025263	187 18
2 1/2	15 1	0 63	0 00020551	184 08
3	28 9	0 34	0 00017278	182 45
3 1/2	19 5	0 19	0 00014883	181 55
4	18 6	0 12	0 00013063	180 09

If all processes involving progesterone 4-^{14}C have gone to com pletion, the *dilution factor* is equal to the secretion rate In these experiments this was approximately the case at the time of the last urine collection

Tables I–V show the specific activity of pregnanediol diacetate and the dilution factors, computed as indicated *above, for each*

correspond very well with the results obtained by Pearlman (1957) Zander (1955 1959) and Solomon *et al* (1962) In our rather small series of experiments we found individual variations in the rate of progesterone production similar to those observed by Solomon *et al* (1962)

Neither this nor earlier investigations on the rate of progesterone production in pregnancy have been able to answer the important question whether there is a fall in progesterone production prior to the onset of labour To elucidate this a large series would be necessary or, still better, repeated determinations of the secretion rate of progesterone in the same individual at different intervals before labour Such an investigation however, will for technical economical and ethical reasons be difficult or impossible to perform

The 3 5 fold increase in progesterone production from midpregnancy to late pregnancy coincides with a rise in spontaneous uterine activity and oxytocin sensitivity (cf Caldeyro-Barcia 1961) Thus in the human being there is no relation between depression of uterine activity and the rate of progesterone production This negative relation may be explained by Csapo s theory about the local effect of placental progesterone the hormone reaches the myometrium without passing the general circulation (Csapo, 1956 1961) This implies that the uterine activity and the endocrine condition of the myometrium are not related to the *amount* of progesterone produced and circulating in the blood but to the *concentration* of progesterone in the myometrium This idea about the importance of the progesterone concentration in the myometrium is in accordance with recent experiments on the activity depressing effect of intra myometrially injected progesterone and synthetic gestagens (Coutinho *et al* 1960 Bengtsson, 1962 Theobald and Lundborg 1962)

In different species of mammals two groups can be distinguished as regards the endocrine control of pregnancy one in which progesterone is produced by the ovaries (*e g* rabbit rat, mouse) and one in which the hormone is manufactured by the placenta (*e g* human sheep guinea pig) This difference in the site of progesterone production seems to be of great significance In the first group progesterone reaches the myometrium via the peripheral

practically gone to completion) Thus the difference between the dilution factors of the first and last urine collection indicates the approximate amount of stored steroid participating in the dilution of the injected progesterone 4-^{14}C The real values of the amount of steroid present in the tissues are probably higher because the dilution factor of the first urine collection is an average obtained after 12 hr of dilution

The average daily progesterone production in the last month of pregnancy was 263 6 ± 80 mg (Table VI) In midpregnancy Ejarque and Bengtsson (1962) found a progesterone production of 75 5 mg/24 hr Thus from midpregnancy to late pregnancy, a 3 5 *fold increase in progesterone production was observed* In the twin case the rate of progesterone production was exactly twice that in the single pregnancies (Table VI) The amount of steroid stored in the tissues was 44 6 mg (Table VI), which is 1 6 times more than in midpregnancy (Ejarque and Bengtsson, 1962)

In this small series of experiments no relation was found between the rate of progesterone production and the time interval to spontaneous labour

Discussion

The results show that a considerable amount of progesterone is produced daily at the end of human gestation, about 260 mg in single pregnancies and 520 mg in a twin pregnancy These values

Table VI *Secretion rate of progesterone and amount of steroid in the tissues in four cases of single pregnancies and one case of twin pregnancy*

Days Before Spontaneous Delivery	Secretion Rate of Progesterone mg day	Steroid in Tissues mg
30	183 00	33 80
15	292 82	39 07
7	361 98	64 40
2 1/2	216 78	41 15
	Mean 263 6 ± 80	44 6 ± 13 5
7 (twins)	520 56	179 72

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7 (twins)	520 56	179 71

within the month before spontaneous delivery was 263 6 ± 80 mg/24 hr In this small number of cases no relation was found between the time interval to delivery and the secretion rate

The secretion rate of progesterone in a twin pregnancy one week before spontaneous delivery was 520 6 mg/24 hr

The significance of the results is discussed

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blood—the hormone is "exogenous" to the uterus, and there is, therefore, a direct relation between the progesterone blood levels and the endocrine condition of the myometrium (cf Mikhail *et al*, 1961) Due to this relation, pregnancy is easily prolonged by progesterone administered into the circulation (Portman, 1934, Csapo, 1955, Fuchs and Fuchs, 1958) In the second group progesterone is produced mainly by the placenta and is, therefore, 'endogenous' to the uterus In these species there is no relation between the following parameters progesterone production, blood progesterone levels, urinary pregnanediol excretion and myometrial activity and reactivity Furthermore, it is impossible or difficult to prolong *normal* pregnancy by systemic administration of progesterone (woman Pose and Fielitz, 1961, sheep Bengtsson and Schofield, 1963, guinea pig Zarrow *et al*, 1963) Thus, in species in which progesterone is manufactured by the placenta, the placental progesterone cannot be replaced by progesterone administered into the general circulation This may explain the failure of conventional gestagen therapy in threatened abortion and premature labour

Theoretically the lack of relation between progesterone production and blood progesterone levels on the one hand and activity and reactivity of the myometrium on the other may be explained in the following way one fraction of the placental progesterone may be transported directly to the myometrium and another fraction be delivered into the blood, where it is rapidly metabolized and inactivated If so, it is evident that only the first mentioned fraction is of significance It would be of great interest to elucidate this hypothetical fraction and its relation to the maintenance and termination of pregnancy

SUMMARY

Progesterone-4-^{14}C was injected *i v* to five women in their last month of pregnancy The secretion rate of progesterone was determined by means of the isotope dilution method from the specific activity of the isolated urinary pregnanediol diacetate The amount of steroid in the tissues and participating in the dilution was calculated in each instance

The secretion rate of progesterone in four normal pregnancies

progesterone as a controlling factor in the maintenance of human pregnancy (Mauzey, 1950, Caldeyro Barcia et al, 1959, Fuchs and Koch, 1963)

Recently it has been postulated by Chermenskaya (1962) that it is the progesterone/œstrogen ratio rather than the exact œstrogen or progesterone concentrations that might initiate spontaneous labour

There is evidence that the effectiveness of various induction procedures reflects the physiological state of the pregnancy If the progesterone/œstrogen ratio, the oxytocinase activity, or the two in combination are determining factors for uterine contractions it would be reasonable to assume that the observed values for these parameters might be correlated with the results of attempts at induction of labour

The present paper contains some preliminary work as an attempt to elucidate the above relations

Material and Methods

The investigations were made on 25 pregnant women 20–40 years of age The indications for induction of labour were prolonged pregnancy *i e* past estimated term (13 cases) *toxæmia* (11 cases) and uterine inertia (1 case) Out of 35 *inductions* 14 were unsuccessful in that neither labour nor even moderate uterine contractions ensued In 6 patients the induction was repeated twice and in one case three times

The standard induction procedure involved the administration of Syntocinon (Sandoz) either by repeated intramuscular injections or as an intravenous drip If the standard induction procedure was unsuccessful it was repeated two days later Amniotomy was avoided or only carried out in the latter stages of labour

Investigation of plasma oxytocinase

Blood samples were obtained at the start of the induction procedure The method for collecting the blood samples and the handling of the plasma is described elsewhere (Fylling 1963) Siliconized glassware and plastic material were used, and the

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PLASMA OXYTOCINASE ACTIVITY, ŒSTRIOL AND PREGNANEDIOL EXCRETION AND THE EFFECT OF INDUCTION OF LABOUR

BY

PETTER FYLLING

*In a recent paper the results of a study of the plasma oxy*tocinase activity during induction of labour were presented (Fylling, 1963) No correlation was found between the oxytocinase *level and the effectiveness of the induction procedure* Therefore, changes in oxytocinase activity may be of minor importance in keeping the uterus at rest during pregnancy

*It has been shown that œstrogens and progesterone have op*posing actions on the myometrium (Csapo 1948, 1956, 1959 and 1961 Bengtsson, 1957, Berde, 1959, Botella-Llusia, 1960, Fuchs and Koch, 1961) The former enhances contraction, whereas the later inhibits this

The changes in hormonal activity during pregnancy are very pronounced and such changes are regarded by many as being responsible for the onset of spontaneous labour (Mauzey, 1950 Csapo, 1956 and 1961 Schofield, 1957, Bengtsson, 1957 Fuchs and Fuchs, 1958, Kumar *et al*, 1962)

The withdrawal of progesterone near term would conveniently explain the onset of labour There is little disagreement with regard to the relaxing effect of progesterone on the myometrium, but the diminution either of progesterone in the blood or of its metabolic product in the urine has not been clearly related to the initation of labour Some workers even tend to dismiss the role of

progesterone as a controlling factor in the maintenance of human pregnancy (Mauzey, 1950, Caldeyro Barcia *et al*, 1959 Fuchs and Koch, 1963)

Recently it has been postulated by Chermenskaya (1962) that it is the progesterone/œstrogen ratio rather than the exact œstrogen or progesterone concentrations that might initiate spontaneous labour

There is evidence that the effectiveness of various induction procedures reflects the 'physiological state' of the pregnancy If the progesterone/œstrogen ratio, the oxytocinase activity, or the two in combination are determining factors for uterine contractions it would be reasonable to assume that the observed values for these parameters might be correlated with the results of attempts at induction of labour

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plasma samples were stored at –20°C for periods up to ten days Duplicate measurements of enzymatic activity were carried out according to the method of Klimek and Pietrycka (1961) The colour densities were measured in a Beckman Spectrophotometer, D U at 565 μ

Investigation of œstriol and pregnanediol

During the 24 hours preceding the instigation of labour, the urine from each patient was collected in glass bottles and sent by mail to the Hormone Laboratory, Haukeland Hospital, where it was investigated The œstrogen determinations were carried out by a modification of the method of Ittrich (1958) This method measures œstriol with satisfactory specificity (Stoa and Thorsen, 1962) Pregnanediol determinations were carried out according to the method of Klopper *et al* (1955)

Results and Discussion

As appears from Table I, the oxytocinase activity in plasma varied considerably However, as shown in a previous paper (Fylling 1963), there was no correlation between the enzymatic activity and the outcome of the induction The mean activity for the group where attempted induction of labour failed tended to be

Table I *Plasma Oxytocinase Activity and Oestriol and Pregnanediol Values The Oxytocinase Activities Are Expressed as Extinction Readings and Œstriol and Pregnanediol as mg/24 hrs The Oestriol Values for the Group in Which Labour Was Induced Are Significantly Higher than the Other (0 01 < P < 0 05)*

	No of Inductions	Range	Mean	$S E_{diff}$	$D S E_{diff}$
Oxytocinase	18 (labour)	226–600	327	0412	601
	9 (no lab)	259–532	352		
Pregnanediol	18 (labour)	16 5–56 4	33 99	4 82	1 21
	10 (no lab)	15 7–59 9	31 68		
Œstriol	21 (labour)	2 1–64 1	19 18	1 83	2 43
	12 (no lab)	4 3–39 2	14 74		
Pregnanediol/ Œstriol ratio	18 (labour)	0 5–11 3	4 12	1 54	0 05
	10 (no lab)	0 6–11 9	4 04		

higher (statistically not significant) than the group resulting in delivery

The observation that there was no correlation between pregnanediol œstriol ratio and the effectiveness of the induction was rather unexpected On the other hand there seemed to be a sig nificant correlation between œstriol excretion and the success of the induction

Furuhjelm (1962), among others, has shown that the œstriol values tend to fall at term, but no regular change has been observed for pregnanediol Green (1950), however, claims that the onset of labour is due to a drop in progesterone, the inhibiting factor

The present data are too small for definite conclusions, but the œstriol values obtained in this series are significantly higher for the group in which labour was induced ($0\ 01 < P < 0\ 05$) On the other hand, the present data does not indicate any correlation between the effect of induction and pregnanediol excretion or pregnanediol/œstriol ratio ($P > 0\ 1$) Also there does not appear to be any correlation between hormone excretion and birth- or placental weight

There is good agreement between the present data and those from other reports as to the œstriol values in toxæmia The lowest values were always found in toxæmia No correlation between oxytocinase or pregnanediol and toxæmia was found

It is well known that there may be great fluctuations in œstriol and pregnanediol excretion therefore the mean value of 10 or more 24 hour urine collections would give a better picture of the hormone excretion For practical reasons, however, it was not possible to collect such samples

SUMMARY

1 Plasma oxytocinase œstriol and pregnanediol were deter mined at the initation of the induction of labour The indications for induction of labour were prolonged pregnancy toxæmia and uterine inertia

2 In the present material there was no correlation between oxytocinase pregnanediol, and pregnanediol/œstriol ratio and the effect of attempted induction of labour On the other hand, there

plasma samples were stored at –20°C for periods up to ten days

Duplicate measurements of enzymatic activity were carried out according to the method of Klimek and Pietrycka (1961) The colour densities were measured in a Beckman Spectrophotometer, D U at 565 μ

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	No of Inductions	Range	Mean	S E diff	D/S E diff
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	10 (no lab)	15 7–59 9	31 69		
Œstriol	21 (labour)	2 1–64 1	19 18	1 83	2 43
	12 (no lab)	4 3–39 2	14 74		
Pregnanediol/Œstriol ratio	18 (labour)	0 5–11 3	4 12	1 54	0 05*
	10 (no lab)	0 6–11 9	4 04		

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was significant correlation between the effect of the induction and œstriol values The œstriol values for the group in which labour was *successfully induced* were significantly higher than in the group where no effect was obtained

3 The present results suggest that œstrogens are more important factors in the initiation of spontaneous labour than either oxytocinase or progesterone

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I am grateful to Ph D N *Norman, M D*, and *Ph D K F Støa* for their valuable suggestions in the preparation of this manuscript I also would like to express my gratitude to K Hoftun Knutsen, M D (*Head of the Department of Obstetrics and Gynæcology*) for his cooperation which was essential to this investigation

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Methods

The subjects selected for this study were women admitted to this hospital for induction of labour The patients were included in this investigation only if they had intact membranes and there were no clinical signs of uterine contractions Before induction their basal uterine activity was recorded for one hour with an external guard ring tocograph (Stanley Cox, Ltd England)

Thereafter a gradient Syntocinon (Sandoz) test was started by giving during alternate minutes an appropriate amount of diluted Syntocinon until an induced contraction was observed The doses of Syntocinon given were 2 5 5 0, 10 0, 15 0, 20 0, 40 0 and 60 0 mU/min The dose of Syntocinon required to induce a contraction was taken as the sensitivity level and the peak uterine pressure as the mechanical response of the uterus to Syntocinon Immediately after the test an amniotomy was performed The time from amniotomy to the delivery of the infant was carefully recorded, but in the subsequent calculations the time was estimated to the nearest half hour All patients who had any operative intervention or treatment with oxytocic agents during labour or at the time of delivery were excluded This selection resulted in a series of 79 women, all of whom gave birth to a living child

Results and Discussion

Table I shows the distribution of the cases according to the mU/min of Syntocinon required to induce contraction and according to the duration of labour It is seen that relative insensitivity to Syntocinon does not necessarily result in a long induction delivery interval Out of the 79 cases 53 gave a reaction with a dose of Syntocinon in the range 5 to 15 mU/min For statistical analysis cases were classified in three groups The groups were positive reaction with 2 5–5 mU/min with 10–15 mU/min, and with 20 mU/min or over They were analyzed in relation to the duration of the labour using the χ^2-test No correlation between the dose required to induce contraction and the duration of labour could be demonstrated ($\chi^2 = 0\ 56$)

Järvinen Pentti A Luukkainen Tapani and Pyörälä Tapani Acta obst et gynec scandinav 43, 64 1964

From the Second Department of Obstetrics and Gynæcology, (Professor P Vara, M D), Central University Hospital, Helsinki

CORRELATION OF SYNTOCINON SENSITIVITY AND UTERINE RESPONSE AT TERM WITH THE COURSE OF INDUCED LABOUR

BY

PENTTI A JÄRVINEN TAPANI LUUKKAINEN AND TAPANI PYÖRÄLÄ

The determination of the optimal time for the induction of labour has been assessed, for example, by studying the condition of the cervix (Cocks, 1955) or by using the Oxytocin Sensitivity Test (Nixon and Smyth, 1957, Smyth, 1958) This latter test was based on the assumption that the oxytocinase activity in blood would diminish with the imminence of labour It was therefore thought possible to build up the higher concentration of oxytocin in the blood stream by giving the same minute amount of oxytocin at a constant rate of 0 01 unit per minute

However, studies on the oxytocin inactivating enzyme have shown that the level of oxytocinase does not decrease with the imminence of labour (Titus *et al* 1960, Tuppy *et al* 1961 Mendez-Bauer *et al* 1961) and the results of the oxytocin sensitivity test do not predict the onset of labour (Goltner, 1959) or the likelihood of success following attempted induction of labour (Järvinen and Huhmar, 1962)

It was assumed by us that oxytocin inactivation could be overcome by giving increasing amounts of oxytocin into the blood stream and that by this method the different levels of oxytocin sensitivity could be determined The results of the study are reported here and the oxytocin sensitivity and the mechanical response of the myometrium are compared with the course of induced labour

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differences between the groups proved to be significant ($\chi^2 = 6.18$, $P < 0.05$)

The progress of labour in these three groups is shown in Fig 1, in which the progressive percentile curves of the groups are presented

SUMMARY

Gradient test doses of Syntocinon were given to 79 women at term until uterine response could be observed After the test labour was induced by artificial rupture of the membranes The relation between the mU/min of Syntocinon required for a positive reaction and the progress of the induced labour was analyzed There was no correlation between the dose and the induction delivery interval

When the cases were grouped according to the peak uterine

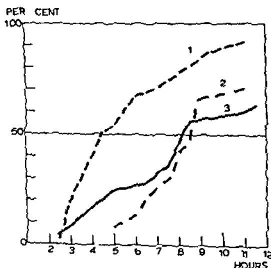


Fig 1 Duration of labour expressed as progressive percentiles in the different groups Group 1 = patients with peak uterine pressure over 22.5 g/cm² after the dose of Syntocinon group 2 = pressure 15.1–22.5 g/cm² group 3 = pressure below 15 g/cm Ordinate Percentage of patients in the group having terminated labour within the stated *time* Abscissa *Hours* Zero point Moment of artificial rupture of membranes

Table I *Distribution of the Series According to Syntocinon Sensitivity in mU/min and Time Interval from Amniotomy to Birth of the Child*

Time Interval in Hours	Syntocinon Sensitivity in mU/min								
	2.5	5.0	10.0	15.0	20.0	40.0	60.0	Insensitive	Total
Under 6	3	5	11	4	4	—	1	1	29
6—12	5	8	5	7	1	3	4	—	33
12—18	1	—	4	2	1	—	—	1	9
18—24	—	2	2	1	1	—	—	—	6
Over 24	—	1	—	1	—	—	—	—	2
Total	9	16	22	15	7	3	5	2	79

Table II *Distribution of the Series According to Uterine Pressure in g/cm² and Time Interval from Amniotomy to Birth of the Child*

Time Interval in Hours	Uterine Pressure in g/cm²								
	Under 7.5	7.6–15.0	15.1–22.5	22.6–30.0	30.1–37.5	37.6–45.0	45.1–52.5	52.6–60.0	Total
Under 6	2	4	3	9	6	1	3	1	29
6—12	1	9	16	4	2	1	—	—	33
12—18	2	4	2	1	—	—	—	—	9
18—24	—	2	2	1	—	1	—	—	6
Over 24	—	1	1	—	—	—	—	—	2
Total	5	20	24	15	8	3	3	1	79

Table II gives the distribution of cases according to the mechanical response of the myometrium to Syntocinon and the induction delivery interval The Table shows that the increased uterine pressure after the test dose of Syntocinon is accompanied by a tendency to a shorter induction delivery interval In the 15 cases where the pressure was over 30 g/cm², only one induction-delivery interval was over 12 hours For statistical analysis the cases were divided into three groups below 15 g/cm², 15.1–22.5 g/cm² and over 22.6 g/cm² The groups represent 31.6 per cent 30.4 per cent and 38 per cent of the cases respectively The percentage of patients who delivered within each period of 30 minutes was calculated The values were then plotted as progressive percentiles and from this curve it was found that the median for the duration of labour in the whole series was about 8 hours The groups were analyzed against this median value using the χ^2 test The

Pehrson, Sigvard L. Acta obst et gynec scandinav 43 69 1964

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SERUM ISOCITRIC DEHYDROGENASE ACTIVITY IN PREGNANT WOMEN AND NEW-BORN CHILDREN

BY

SIGVARD L PEHRSON

The observation that the placenta is rich in isocitric acid dehydrogenase (ICD) is of great interest to the obstetrician

In a preliminary report Dawkins, MacGregor and McLean (1959) claimed to have shown an increase in ICD during pregnancy complicated by pre-eclampsia The source of the increased content of ICD in serum was held to be placenta infarcts Normally, serum contains only a trace of ICD, and its increase is found solely in diseases associated with liver cell damage (Sterkel, Spencer, Wolfson and Williams-Ashman, 1959, Kerppola, Nikkilä and Pitkänen 1959) In normal pregnancy no change is found to occur in the ICD content (Wolfson and Williams-Ashman, 1957, Dawkins and Wigglesworth, 1961 Jeacock, Morris and Plester 1962 Little and Kirpalani, 1962)

There have been many investigations into the metabolism of enzymes during pregnancy Little (1959) studied lactic dehydrogenase (L D) and found normal values During delivery the content of L D may increase Serum glutamic oxalacetic trans aminase (SGOT) may occasionally be increased in pre-eclampsia (Borglin 1958) Borglin assumed that the placenta was the source of this increase In order to answer the problem of the significance of an increase in the ICD content in the mother s serum an attempt has been made in this work to solve a number

pressure recorded after Syntocınon, a posıtıve correlatıon was found between the progress of labour and the magnıtude of the mechanıcal response of the myometrıum

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SIGVARD L. PEHRSON

The observation that the placenta is rich in isocitric acid dehydrogenase (ICD) is of great interest to the obstetrician

In a preliminary report Dawkins, MacGregor and McLean (1959) claimed to have shown an increase in ICD during pregnancy complicated by pre-eclampsia The source of the increased content of ICD in serum was held to be placenta infarcts Normally, serum contains only a trace of ICD and its increase is found solely in diseases associated with liver cell damage (Sterkel, Spencer, Wolfson and Williams Ashman, 1959 Kerppola, Nikkilä and Pitkänen, 1959) In normal pregnancy no change is found to occur in the ICD content (Wolfson and Williams-Ashman, 1957, Dawkins and Wigglesworth 1961, Jeacock, Morris and Plester 1962, Little and Kirpalani, 1962)

There have been many investigations into the metabolism of enzymes during pregnancy Little (1959) studied lactic dehydrogenase (L D) and found normal values During delivery the content of L D may increase Serum glutamic oxalacetic transaminase (SGOT) may occasionally be increased in pre-eclampsia (Borglin 1958) Borglin assumed that the placenta was the source of this increase In order to answer the problem of the significance of an increase in the ICD content in the mother s serum an attempt has been made in this work to solve a number

of basic problems Is there any transmission of ICD from the mother to the foetus or the converse? What is the normal value for new-born children? Have the new-born children of mothers with toxæmia higher values than those children who have healthy mothers?

Method

Blood samples were taken from an ante-cubital vein in the mother and from the umbilical cord immediately after delivery Great care was taken to avoid hæmolysis Samples showing hæmolysis were discarded The serum was separated off within an hour after the samples were drawn If the investigation could not be carried out on the same day as the samples were taken, these were kept in a refrigerator at +4° At this temperature the ICD content in a sample is constant for several weeks (Bowers, 1959) The ICD content was determined according to Wolfson and Williams-Ashman The technique is described in greater detail in the Sigma Medical Bulletin no 150 (June 1959) Two determinations were made on nearly all the samples

Technique

The components[1] were mixed in a test tube The test tube was then placed for some minutes in a water-bath at a constant temperature of +25° C Then 1 ml of serum was added and a stop watch was started The optical density (O D) was read in a Bechman B Spectrophotometer at 340 mμ at 3 minutes intervals for 30 minutes Water was used as a reference The changes in the O D were read every 3 minutes The results were expressed in the same units as were used by Karman, Wroblewsky and La Due (1955) for transaminase (Karman units U_K) A unit is defined as the quantity of enzyme which produces a change in the optical density (Δ O D_{340}) in 0 001/minutes per ml serum with wave length of 340 mμ A Wolfson

[1] 1 1 00 ml TRIS Buffer (pH 7 5)
2 0 50 ml TPN (tri phospho-pyridine nucleotide)
3 0 50 ml 0 02 M $MnCl_2$ solution
4 0 10 ml Isocitrate solution

and Williams Ashman unit ($U_{W W A}$) of serum ICD is defined by Wolfson and Williams Ashman as that quantity of enzyme which produces one millimicromole TPNH[1] per ml serum per hour at a temperature of +25° C The changes observed per minute in the O D are converted to $U_{W W A}$ by multiplying by 30,000 Wolfson and Williams Ashman units are converted to Karman units by dividing by 30

$$\frac{U_{W W A}}{30} = U_K$$

Results

Normal pregnancy at delivery

Maternal venous blood and umbilical venous cord blood from the veins was taken at delivery in 30 cases The mean value for the mothers vein serum was 7 65 $U_K \pm$ 5 46 The upper limit with 2 S D was 18 5 U_K The ICD content in the venous blood was 8 72 $U_K \pm$ 5 63 The upper limit with 2 S D was 20 0 U_K The difference between the means was not statistically significant On average the ICD content in the child s serum was 1 16 U_K higher than that of the mother This difference in not statistically significant t = 0 90 (t greater than or equal to 2 045 gives significance on the 5% level) It was not possible to show any correlation between the ICD content in the mother s serum and the child s serum (r = 0 179)

Normal new born children

Umbilical cord blood was collected from 63 new born children The deliveries were normal Mothers and children were all healthy

The mean ICD activity in the venous blood of the umbilical cords of these children was 8 12 $U_K \pm$ 5 48 The upper limit with 2 S D was 19 1 in this series In 8 cases the veins and arteries of the umbilical cords were punctured separately and the blood samples from both these vessels were analysed Venous blood was taken from the mothers at the same time

[1] (reduced tri phospho-pyridine nucleotide)

Table I *Serum ICD Content at Delivery*

Case	Maternal Vein	Umb Cord Vein
Case 1	6 2	3 8
2	6 2	12 3
3	3 7	2 8
4	9 8	17 2
5	6 4	5 9
6	2 6	5 6
7	6 0	16 9
8	7 5	2 2
9	8 2	3 0
10	7 8	15 6
11	3 5	8 4
12	15 1	9 4
13	3 9	5 9
14	3 3	2 2
15	3 3	14 2
Case 16	25 5	16 6
17	8 3	3 3
18	20 8	10 8
19	6 8	16 7
20	10 6	6 8
21	5 4	5 7
22	11 1	12 4
23	7 8	3 4
24	10 9	5 2
25	6 4	2 1
26	8 3	3 1
27	18 8	1 0
28	7 9	12 8
29	17 2	1 4
30	2 4	1 8
Mean	8 72	7 65
SD	5 63	5 46

Table II *Serum ICD Content in Umbilical Cord Venous Blood Normal Delivery Healthy Mothers and Children*

Case		Case		Case		Case	
Case 1	2 9	Case 17	6 8	Case 33	5 8	Case 49	5 4
2	5 6	18	6 5	34	5 1	50	6 6
3	4 8	19	6 2	35	7 1	51	7 3
4	6 4	20	5 2	36	7 7	52	5 1
5	8 6	21	15 6	37	11 3	53	5 1
6	5 2	22	6 6	38	13 5	54	12 2
7	4 1	23	42 2	39	5 2	55	5 8
8	7 1	24	2 7	40	7 4	56	5 9
9	13 9	25	13 0	41	6 0	57	5 6
10	5 1	26	5 7	42	10 6	58	6 0
11	6 4	27	7 2	43	7 3	59	7 3
12	6 1	28	6 6	44	5 2	60	7 5
13	5 8	29	16 8	45	8 0	61	6 0
14	12 5	30	7 7	46	13 2	62	10 1
15	6 7	31	6 6	47	7 4	63	5 5
16	6 9	32	5 0	48	11 0	64	—

Mean 8 12 SD 5 48

Table III Serum ICD Content of Arterial and Venous Blood in Umbilical Cord and in Venous Blood of Mother

	Artery	Vein	Maternal Vein
Case 1	2 6	4 0	2 6
2	4 5	5 2	1 9
3	6 1	6 4	8 8
4	14 1	14 4	4 5
5	3 9	4 0	4 7
6	4 2	4 0	2 2
7	2 6	2 3	2 0
8	4 1	3 5	3 6
9	—	8 1	4 7
Mean	5 25	5 77	4 10

Table IV Serum ICD Content of Venous Blood from Toxæmic Mothers and of Venous Blood in Umbilical Cord of Their Healthy Children

	Diagnosis	Materal Vein	Umb Cord Vein
Case 1	Severe pre eclampsia	5 5	14 7
2		8 0	9 1
3		26 7	36 1
4		3 1	7 9
5	Mild	49 1	6 1
6		5 0	2 6
7		5 1	5 8
8		9 2	4 0
9		4 7	9 2
10	Albuminuria	9 5	29 1
11		6 0	23 6
12		5 1	1 7
	Mean	11 79	13 03
	S D	13 25	5 46

The mean for the arteries was 5 25 U_K and for the veins 5 77 U_K and for the mothers 4 01 U_K There was no significant difference between these values

Normal new born children of mothers with toxæmia

Venous blood and umbilical-cord blood at delivery was taken from 9 mothers with mild or severe pre-eclampsia and from 3 cases with albuminuria and normal blood pressure

Table V *Serum ICD Content of Umbilical Cord Blood from New born Children of Mothers with Toxæmia*

Case	ICD value	Diagnosis
1	3 6	Severe pre eclampsia
2	6 2	" " "
3	2 1	" "
4	4 5	Mild " "
5	7 7	Albuminuria
6	33 7	"

One mother with severe pre-eclampsia had a high serum ICD value (26 7 U_K) Her child also had a high value (36 1 U_K) A mother with mild pre-eclampsia had a high value, but her child showed normal activity In 2 cases with albuminuria the new born children had high values, whereas the mothers had quite normal values All the placentae in this series were macroscopically normal The difference between the means for toxæmic mothers and normal mothers (4 14 U_K) is not statistically significant In 6 cases where the mothers had toxæmia, only the venous blood of the umbilical cords was investigated One of these cases showed a high value, above the upper limit for healthy new born children (33 7 U_K) The remaining children had normal values

New-born children with abnormalities

Venous blood was collected from the umbilical cords of new-born children with various diseases in either the children or the mothers

In one case where the mother had an accidental hemorrhage in the final trimester of pregnancy there was a high value exceeding the upper limit for normal newborns (22 1 U_K) All the other children had normal values

Conclusions

If placental infarcts are the source of the increased ICD content in the mother's venous blood, which is generally considered to be the case, then vascular damage in the placenta should also give rise to increased levels in the serum of the fœtus If the placental damage affects only the maternal part of the placenta

Table VI *Serum ICD Value in Umbilical Cord Venous Blood from Newborn Children with Abnormalities*

Abnormality	ICD Value
Fœtal asphyxia	43
	47
	80
	47
	132
Pulmonary atelectasis	95
Immaturity	69
	89
Prematurity	89
Placental dystrophia	60
Immaturity + anencephaly	38
Prematurity + microcephaly	170
Icterus neonatorum	132
Melæna neonatorum	91
Hæmorrhage during pregnancy	221
Syphilis (mother)	109

Birthweight less than 2500 g pregnancy duration more than 38 weeks

then only the mother s ICD content in the serum should rise, and if the placental damage affects merely the fœtal part, the ICD content in the serum of the fœtus ought to increase separately This investigation has shown that the ICD content in the mother s venous blood and umbilical-cord blood are normal and the same size There was no statistically significant difference *Little* and Kirpalani (1962) found a significantly higher ICD value in the venous blood of newborn infants When investigating SGOT Borglin was able to show, among other things that the child s enzyme activity is about twice as great as that of the mother This can perhaps be explained by the higher molecular weight of SGOT No correlation between the mother s ICD content and that of the child could be shown to exist This indicates that the mother s and the child s ICD enzymes are entirely separate from one another The placenta appears to offer a complete barrier to ICD The ICD content in the arteries and vein of the same umbilical cord is also the same In an earlier

investigation I was able to show that SGOT is significantly higher in the arteries than in the vein of the same umbilical cord Nor does the ICD appear to be broken down during its passage through the placenta

In some cases of toxæmia, increased serum values are found in the mothers, whereas in other cases these values are quite normal In one case high values were demonstrated in both the mother and the fœtus In some cases high values were shown to be present in either mothers or fœtus This also indicates that the enzyme systems are separate from one another Investigations, with random samples, of the ICD content of the mother's venous blood seem to have a very limited value

SUMMARY

The serum ICD activity has been studied in the mother s serum and in the umbilical cord blood at delivery The mean ICD value in the serum of healthy mothers with normal deliveries was 7 65 $U_K \pm 5\ 46$ (229 $U_{WWA} \pm 164$ U_{WWA}) The upper limit with 2 S D was 18 5 U_K (555 U_{WWA}) The mean ICD activity in the umbilical cord blood of new born healthy children, after normal delivery, was in one series 8 72 $U_K \pm 5\ 63$ (262 $U_{WWA} \pm 169$ U_{WWA}) The upper limit with 2 S D was 20 0 U_K (600 U_{WWA}) No statistically significant difference could be shown to exist between arteries and veins in the same umbilical cord There was no statistically significant difference in ICD activity between mother and child In one series of 12 patients with toxæmia, 2 mothers had high values at delivery (16 6 per cent) The new-born children of mothers with toxæmia had high values in 3 cases (25 per cent) Of 6 new born children of mothers with toxæmia in another series one child had a high value, above the upper limit for healthy new born children (16 6 per cent) In one case with accidental hæmorrhage during pregnancy, the mother s serum was found to have a normal value at the time of the hæmorrhage and the umbilical-cord blood of the new-born child had a high value The placenta was quite normal

Random sample investigations of the ICD content appear to have a very limited value

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MICROLITER DETERMINATIONS OF TOTAL AND DIRECT BILIRUBIN, ALKALINE PHOSPHATASE, POTASSIUM, SODIUM AND UREA NITROGEN IN BLOOD PLASMA DURING THE EARLY NEONATAL PERIOD

BY

BERTIL THALME

In a previous paper studies of the neonatal blood concentrations of calcium, chloride, cholesterol, inorganic phosphorus and total protein were reported (Thalme, 1962) The investigation was made with the ultramicrotechnique of Sanz (1957, 1959) as developed by Beckman/Spinco

The reliability of chemical methods on a microliter scale has been tested in a preliminary study by Thalme and Aberg (1961) and recently a thorough study of this technique has been carried out with the introduction of some new methods and slight changes in recommended methods (Thalme, 1963)

In the present study it was decided to complete the investigation by measuring the concentrations of total and direct bilirubin, alkaline phosphatase, potassium, sodium and urea nitrogen in the early *neonatal period* Reference values were thus obtained for investigations on premature, postmature and diseased newborn infants and fœtuses

Material and Methods

Two groups of healthy full term breastfed newborn infants from the maternity wards of Karolinska Sjukhuset were studied

In a serial study 10 newborn infants were investigated within the first half hour of life, after 4 hours, 1 day, 2 days and 4 days In a few cases the levels of bilirubin and alkaline phosphatase were also determined between the fourth and the ninth day of life

Single determinations were done on 127 newborn infants at various times after birth, up to 12 days of age Bilirubin, total and direct and alkaline phosphatase were determined on one sample, while potassium, sodium and urea nitrogen were determined on a second sample The newborn infants were grouped according to age as follows 0–6 hours after birth, 6–12 hours, 12–24 hours, 1–2 days 2–3 days, 3–4 days, 4–6 days and 6–12 days

Blood samples were obtained by pricking the heels as described by Pincus *et al* (1956) The blood was collected in plastic test tubes For comparison blood was also taken by finger prick from students and members of the laboratory staff All determinations were made in duplicate from the same blood sample Methods used were microliter adaptations of well known routine methods, as presented in Table I Numbers of subjects are indicated and also the volume of sample required

Bilirubin total and direct was determined according to the

Table I

Analysis	Ultramicro-Adaption of the Method of	Amount µl	Single Determination	Serial Study	Adults
Bilirubin total and direct	Malloy and Evelyn	10	127	9	23
		10	120	9	19
Alkaline phosphatase	Bodansky s method modified by Natelson	10	111	10	21
Potassium	Kaplan and del Carmen	20	101	7	22
Sodium	Kaplan and del Carmen	20	112	8	22
Urea nitrogen	Johansson (modified ureasemethod)	10	96	8	19

Total bilirubin includes both direct and indirect reacting fractions The direct which is the glucuronide of bilirubin and is formed in the liver is water-soluble and distinguished from the indirect fraction bilirubin attached to

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	Age of Newborn Infant								Adult
	0-6 h	6-12 hr	12 24 hr	1 2 days	2 3 days	3 4 days	4-6 days	6-12 days	
Bilirubin total mg/100 ml									
n	16	13	15	16	21	18	18	10	23
M	2 45	2 77	4 63	5 60	5 72	5 77	2 53	2 44	0 71
s	1 02	0 85	1 46	2 15	2 69	2 02	1 56	1 13	0 17
M±k×s	4 73 0 17	4 9-0 ,6	7 96-1 31	10 43 0 77	11 44-(-0 01)	10 20-1 34	5 95 (-0 89)	5 29-(-0 41)	1 07-0 34
Bilirubin direct mg/100 ml									
n	14	9	14	16	21	18	18	10	19
M	0 42	0 34	0 46	0 44	0 45	0 43	0 39	0 36	0 13
s	0 09	0 14	0 12	0 08	0 13	0 16	0 13	0 14	0 10
M±k×s	0 63-0 20	0 70-(-0 02)	0 73-0 19	0 63-0 25	0 72-0 17	0 79-0 07	0 67-0 12	0 71-0 00	0 35-(-0 09)
Alkaline phosphatase units									
n	17	10	16	15	10	15	17	11	21
M	8 01	6 57	7 67	7 59	6 72	7 11	7 44	7 35	2 49
s	1 95	1 07	1 45	2 19	2 74	2 22	3 19	2 32	0 78
M±k×s	12 34-3 69	9 29-3 85	10 93-4 40	12 58-2 61	13 66-(-0 22)	12 15-2 06	14 51-0 36	13 07-1 63	4 16-0 83
Potassium mEq/liter									
n	18	10	14	11	11	10	17	10	22
M	5 71	5 70	5 71	5 92	5 80	5 90	5 73	5 73	4 90
s	0 41	0 49	0 51	0 50	0 40	0 54	0 55	0 46	0 24
M±k×s	6 62 4 81	6 04-4 45	6 88-4 53	7 15-4 70	6 78-4 81	7 25-4 54	6 95-4 51	6 89-4 57	5 41-4 39
Sodium mEq/liter									
n	17	15	15	15	13	12	15	10	22
M	139 4	137 9	139 5	143 0	143 5	142 4	141 0	142 1	137 0
s	4 7	2 8	4 3	3 4	2 2	3 7	2 9	3 8	2 2
M±k×s	149 9-128 9	144 3-131 5	149 3-129 7	150 8-135 2	148 7-138 3	151 4-133 4	147 7-134 4	151 7-132 4	141 6-132 3
Urea nitrogen mg/100 ml									
n	12	11	10	12	14	12	13	12	19
M	10 5	12 8	12 6	14 9	16 9	13 7	11 1	10 6	10 1
s	2 2	2 9	2 2	3 5	6 8	5 4	4 4	2 2	1 5
M±×s	15 9-5 1	19 9-5 6	18 1-7 1	23 4-6 4	32 7-1 1	26 7-0 7	21 4-0 8	16 0-5 3	13 3-6 9

n=number of investigated newborns M=mean value s=standard deviation k=a constant from Table A 16 in *Introduction to Statistical Analysis* by Dixon & Massey

M±k×s=the 90 % limits for a 90 % confidence

method of Malloy and Evelyn (1937) modified so that only 10 μl samples were required for the analysis

For the determination of alkaline phosphatase a microliter procedure was designed based on Natelson's modification (1961) of Bodansky's method (1933) In the method employed 10 μl samples were used, 20% trichloroacetic acid was used to stop incubation and the extinction read at 650 mμ

The determinations of potassium and sodium were made according to the method of Kaplan and del Carmen (1956) using an Eppendorf Flame Photometer adapted for microliter volumes All material in contact with the sample was made of plastic and great care was taken to use only plasma free from hæmolysis

For determination of urea nitrogen a urease method developed by Johansson (1962) was modified to microliter volumes

Further details concerning the microliter methods used, their accuracy and the modifications employed will be presented in another paper (Thalme, 1963)

The error of the methods was estimated by duplicate analysis from the same blood sample obtained from each of the newborn infants 1–4 days of age in the single examination study The error in the methods is presented in Table II

The statistical calculations were made by standard methods[1]

Table II

Analysis	Error of Method n	s
Bilirubin total mg/100 ml	54	0 20
Bilirubin direct mg/100 ml	54	0 06
Alkaline phosphatase units	38	0 34
Potassium mEq/liter	32	0 05
Sodium mEq/liter	30	0 73
Urea N mg/100 ml	37	0 40

$$s = \sqrt{\frac{\Sigma d^2}{2n}}$$

albumin, which is water insoluble but soluble in alcohol Indirect reacting bilirubin is measured as the difference between total and direct reacting bilirubin

[1] The statistical treatment of the results has been carried out by Dr Staffan Ekblom of the Statistical Research Group of the University of Stockholm

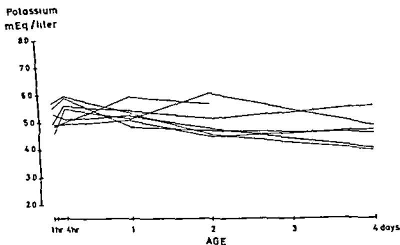


Fig 3 Potassium in 7 children at various times after birth

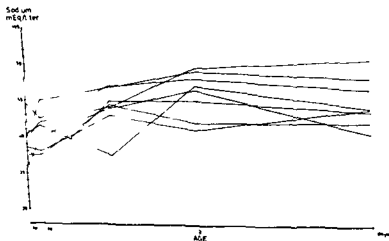


Fig 4 Sodium in 8 children at various times after birth.

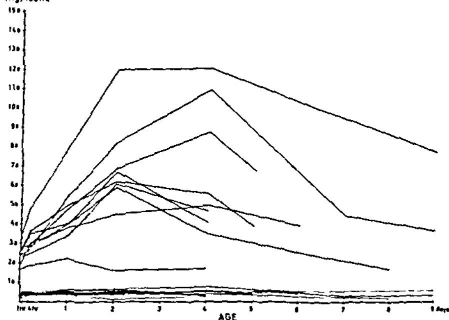


Fig 1 Bilirubin, total and direct, in 9 children at various times after birth The lower 9 lines are the direct readings

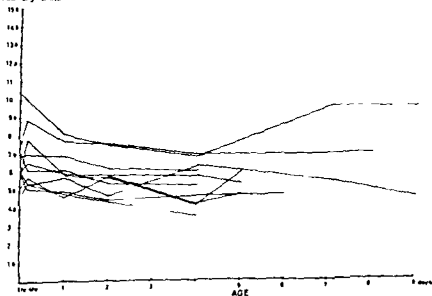


Fig 2 Alkaline phosphatase in 10 children at various times after birth

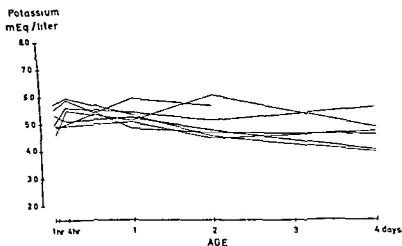


Fig 3 Potassium in 7 children at various times after birth

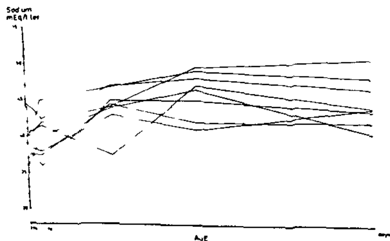


Fig 4 Sodium in 8 children at various times after birth.

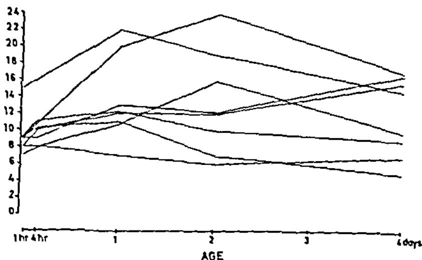


Fig 5 Urea nitrogen in 8 children at various times after birth.

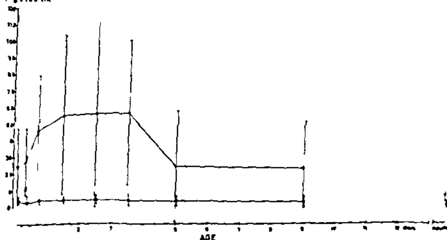


Fig 6 Total bilirub in 127 and direct bilirubin in 120 children at various times after birth. The mean value is given together with the 90% limits for a 90% confidence

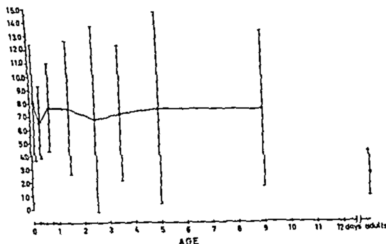


Fig 7 Alkaline phosphatase in 111 children at various times after birth. The mean value is given together with the 90% limits for a 90% confidence

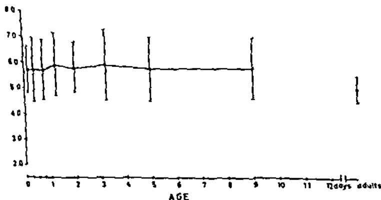


Fig 8 Potassium in 101 children at various times after birth The mean value is given together with the 90% limits for a 90% confidence

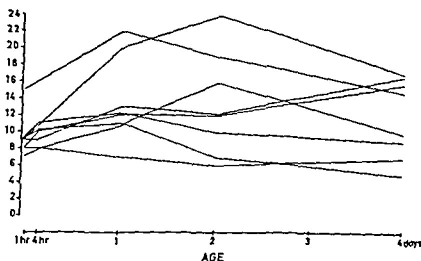


Fig 5 Urea nitrogen in 8 children at various times after birth

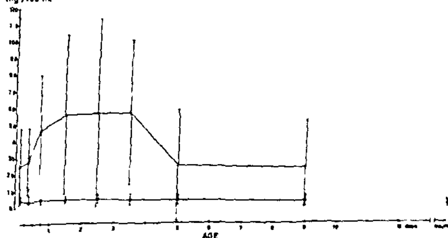


Fig 6 Total bilirubin in 127 and direct bilirubin in 120 children at various times after birth *The mean value is given together with the 90% limits for a 90% confidence*

Results

In the serial study the results for bilirubin, total and direct, alkaline phosphatase, potassium, sodium and urea nitrogen respectively are given in Figs 1–5

The results of the single determinations of bilirubin, total and direct alkaline phosphatase, potassium, sodium and urea nitrogen are given in Figs 6–10 and Table III

Figs 6–10 present the results in graphic form Each point represents the mean value of each age group from 0–6 hours after birth to 6–12 days of life The vertical lines indicate the 90% limits for 90% confidence In order to indicate trends the mean values of the different age groups have been connected For comparison the adult values are also shown

Total bilirubin

The total bilirubin level increased rapidly during the first two days of life to a maximum value between the second and fourth day of life after which a successive decrease of concentration occurred during the remaining time periods studied

The longitudinal study showed two different peaks The lower concentrations of bilirubin tended to reach their peak at two days while the higher concentrations tended to reach their peak at four days of age

Direct bilirubin

The direct bilirubin level remained constant during the observed time periods but showed higher values than in adults

Alkaline phosphatase

The newborn infants had a concentration of alkaline phosphatase about three times that of adults The mean values in the early neonatal period were fairly constant

Potassium

The newborn infants had a potassium level above that found in adults The observed mean values during the early days of life were however, fairly constant

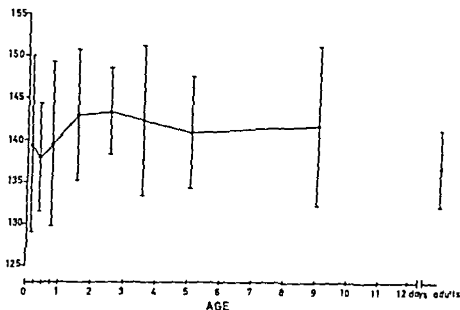


Fig 9 Sodium in 112 children at various times after birth The mean value is given together with the 90% limits for a 90% confidence

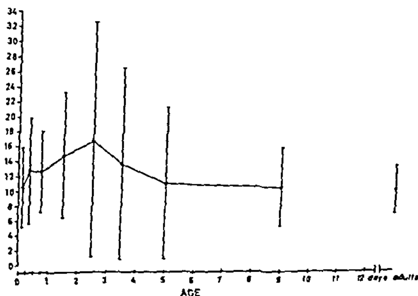


Fig 10 Urea nitrogen in 96 children at various times after birth The mean value is given together with the 90% limits for a 90% confidence

Analysis		Authors	Age in Days	n	Mean	Range	Source	Method
Bilirubin total	mg/100 ml	Hsia Allen Diamond and Gellis 1953	at birth	12	2 2	1 4—3 2	cord blood	Hsia Hsia Gellis
			1	11	5 7	3 4—7 4	capillary blood	
			2	12	7 1	3 1—12 4		
			3	12	6 6	0 6—13 2		
			4	12	4 9	0 0—12 3		
			5	10	4 2	0 9—9 5		
Bilirubin direct	mg 100 ml	Schellong C 1962	at birth	174	1 43	(s=0 49)	capillary blood	Jendrassik Grof
			1	242	3 95	(s=1 58)		
			2	242	5 20	(s=2 62)		
			3	242	5 89	(s=3 46)		
			4	242	5 73	(s=3 87)		
Alkaline phosphatase	units	v Sydow G 1946	1	22	8 35	(s=2 44)	capillary blood	Buch Buch
			2	22	8 01	(s=2 23)		
			3	23	7 43	(s=2 26)		
			4	19	7 02	(s=2 60)		
			5	22	6 95	(s=2 33)		
			6	21	7 13	(s=2 31)		
Potassium	mEq/liter	Pincus Gittleman Saito and Sobel 1956	1	12	5 4	4 46—6 80	capillary blood	
		Strengers Maas Rottinghuis and Fehmers 1954	1	32	5 1		capillary blood	Strengers & Klinkenbergh
			2	32	4 0			
			3	32	4 8			
			5	32	4 8			
			[illegible]	32	4 6			
			adults	25	4 8			
Sodium	mEq/liter	Strengers Maas Rottinghuis and Fehmers 1954	1	32	141		capillary blood	Strengers & Klinkenbergh
			2	32	138			
			3	32	142			
			5	32	143			
			7	32	140			
			adults	25	140			
Urea nitrogen	mg/100 ml	McCance and Widdowson 1947	at birth	12	18 9	8 0—28 8	capillary blood	Lee Widdowson
			3	12	29 1	18 5—39 6		
			6	12	19 7	9 9—27 4		
			8	12	16 8	10 4—25 0		
		Pincus Gittleman Saito and Sobel 1956	1	12	15	7 0—30 0	capillary blood	

Sodium

The level of sodium was of the same magnitude both in newborn infants and adults The values remained constant during the observed time period

Urea nitrogen

The concentration of urea nitrogen increased slightly during the first three days of life after which it successively decreased during the 6–12 days to levels normal for adults The mean values at birth and at 6–12 days of age were similar to those in adults

Discussion

In this investigation the ultramicrotechnique of Sanz (1957, 1959) which had been found to be very useful in the previous investigations (Thalme and Aberg, 1961, Thalme, 1962, 1963) was employed

For comparison with the findings of other investigators with the present study some of the values previously reported for bilirubin, alkaline phosphatase, potassium, sodium and urea nitrogen in capillary blood are shown in Table IV

Bilirubin

The bilirubin content of plasma in the newborn infant has been studied extensively by numerous investigators (Davidson *et al*, 1941, Hsia *et al*, 1953, Schellong, 1962, Vest, 1959, Waugh *et al*, 1940, Ylppo, 1913) and the same pattern of bilirubin level in the neonatal period has been described During the first days of life an increase to a peak between the second and fourth day of life is followed by a gradual decline to normal values by the third week The present findings are in agreement with this Different authors have found the bilirubin peak to occur either on the second, third or fourth day of life Hsia *et al* (1953) claimed that the bilirubin peak occurred at two days of age, whereas Schellong (1962) reported a maximum concentration on the third day and Vest (1959) and Waugh *et al* (1940) found the highest bilirubin value on the fourth day of life The maximal concentration obtained by all these authors

greatly probably due to different methods employed, slight hæmolysis in drawing the sample and some transfer of potassium from red blood cells to plasma when the blood sample is left at room temperature (Brenner and Gralka, 1953)

Urea nitrogen

The present investigation showed a more marked fluctuation in urea nitrogen level during the early days of life than was reported by Sherman *et al* (1925) The obtained values for urea nitrogen are in good agreement with those reported by McCance and Widdowson (1947), Pincus et al (1956) and Sedgwick and Ziegler (1920) Lucas *et al* (1921) studied the urea nitrogen concentration in newborn infants from a few hours after birth to the twelfth day post partum and reported an increase during the first day of life followed by a definite drop the next day to a fairly constant level for the remaining periods investigated McCance and Widdowson (1947) made serial determinations on 12 normal newborn infants at birth after 3 days, 6 days and 8 days They observed a higher level of blood urea on the third day of life than at birth or on the sixth and subsequent days

SUMMARY

Microliter chemical methods according to Sanz ultramicrotech nique were used for the determination of bilirubin, total and direct alkaline phosphatase potassium sodium and urea nitrogen in blood plasma from newborn infants and adults

During the first days of life an increase of total bilirubin and urea nitrogen were observed while the values for alkaline phos phatase potassium and sodium remained fairly constant during the observed time period

Acknowledgement

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was, however, similar That larger concentrations of bilirubin tend to reach their peak values later than lower concentrations has been shown by Ylppo (1913) and Davidson et al (1941) The latter computed medians as a measure of tendency and found that "Whereas the first decile, the first quartile and the median all reach their peak levels of the 2nd day of life, the third quartile and ninth decile attain their peaks on the 4th day "

Alkaline phosphatase

The present values for the concentration of alkaline phosphatase during the early neonatal period are in good agreement with those reported by Barnes and Munks (1940), Christiansson and Josephson (1960), Mulay and Hurwitz (1937) and v Sydow (1946) Some investigators (Christiansson and Josephson (1960), Stearns and Warweg (1933)) have found a similar concentration of alkaline phosphatase during the first week of life and in adults Others (Bodansky and Jaffe (1933), Mulay and Hurwitz (1937)) have reported adult values of the same range as the present study

Potassium and sodium

The values for potassium and sodium in the current study are of the same order as some of the values reported in the literature Apart from slight variations during the first week of life the sodium content does not differ greatly from that in adults (Overman et al (1951), Pincus et al (1956), Strengers et al (1954) and Murtagh et al (1957))

The potassium level on the other hand showed higher values than in adults, confirming other reports (Pincus et al, 1956, Österlund, 1955) Pincus et al (1956) found an average concentration of 5 4 mEq/liter on the first day of life Österlund (1955) found the neonatal potassium level to be approximately 1 mEq/liter higher than the maternal Edelstein and Ylppo (1920) and Widdowson and McCance (1956) found a remarkably high concentration of potassium in infants compared to adults, while Overman et al (1951), on the other hand, found little difference between them The reported values vary

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THE EFFECT OF PROSTAGLANDIN E_2 AND E_3 ON THE HUMAN UTERUS AND THE FALLOPIAN TUBES IN VITRO

BY

F SANDBERG A. INGELMAN SUNDBERG AND G RYDÉN

Bergstrom *et al* (1960 1962) have recently shown that the biological activity of the "prostaglandin" extracts of sheep vesicular glands is due mainly to three related components, Prosta glandin E_1 E_2 and E_3 (PGE_1 PGE_2 PGE_3) All these three prostaglandins have been isolated from human seminal plasma (Berg strom and Samuelsson 1962 Samuelsson 1963)

The structures of Prostaglandin E_1 E_2 and E_3 are shown in fig 1 They are all derivatives of a C_{20} acid prostanoic acid containing a cyclopentan ring PGE_1 has one PGE_2 two and PGE_3 three double bonds

The effect of Prostaglandin E_1 on the human uterus and Fallopian tube in vitro has been studied in a previous paper (Sandberg *et al* 1963)

This paper deals with the effects of Prostaglandin E_2 and E_3 These substances were kindly supplied by Prof S Bergstrom and Dr B Samuelsson Stockholm

Material and Methods

The material was obtained at hysterectomies and salpingectomies The Fallopian tubes were collected from 41 patients and the myometrial tissue from 38 patients

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II *Uterus*

The results obtained are listed in Table III PGE₂ exerts an inhibitory effect This is shown by a decrease in all parameters both in the corpus and in the isthmus in the dose range used The isthmus is more sensitive to PGE₂ than the corpus as shown by a higher incidence of response There is no pronounced difference between the phases

Prostaglandin E_3

I *Fallopian tubes*

The results concerning the effects of PGE_3 are listed in Tables IV and V Within the range of dosage there were no qualitative differences In the lowest dose, however, there was a lower incidence of response

PGE_3 produces an inhibitory effect on all four segments both in the proliferatory and secretory phases

II *Uterus*

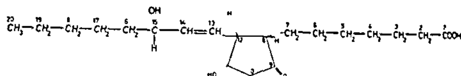
The results obtained are listed in Table VI PGE_3 exerts as a rule an inhibitory effect both on the corpus and on the isthmus This action is most pronounced concerning the parameters frequency amplitude and amplitude maximum The isthmus is more sensitive than the corpus as shown by a higher incidence of response No pronounced difference between the cyclical phases is observed

Discussion

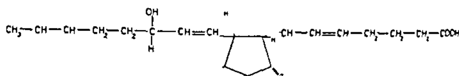
The effects of PGE_1 PGE_2 and PGE_3 on human Fallopian tube and uterus are described in a previous paper (Sandberg *et al* 1963) and in this publication

All three substances have been used in the range of dosage of 0 006—0 050 γ/ml Common to all doses was the fact that no qualitative differences in response could be demonstrated In the lowest dose however there was a decreased incidence of response throughout

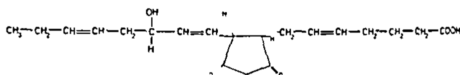
The specific effect of PGE_1 is an increase in tonus and amplitude maximum in the proximal part of the tube (segment 1)



Prostaglandin E_1 11α,15-dihydroxy-9-keto-prost-13-enoic acid



Prostaglandin E_2 11α,15-dihydroxy-9-keto-prost-5,13-dienoic acid



Prostaglandin E_3 11α,15-dihydroxy-9-keto-prost-5,13,17-trienoic acid

Fig 1

The experimental conditions and the evaluation of the results obtained were identical with those described for Prostaglandin E_1 in this journal (Sandberg *et al*, 1963)

PGE_1, PGE_2 and PGE_3 were all given in doses of 0·006—0·05 γ/ml

Results

Prostaglandin E_2

I *Fallopian tubes*

The results concerning the effects of PGE_2 in the proliferatory and secretory phases are given in Tables I and II Within the dose range used there were no qualitative differences in response In the lowest dose, however, there was a lower incidence of response

Prostaglandin E_2 exerts a stimulatory effect on the proximal part of the tube (segment 1), demonstrated by increase in tonus and in amplitude maximum In the rest of the tube PGE_2 produces an inhibitory effect This difference in response between segment 1 and the rest of the tube is however, most pronounced in the secretory phase

Table I *In vitro Effects of Prostaglandin E_1 Tested on the Longitudinal Musculature of the Fallopian Tubes from 16 Women in the Proliferatory Phase*

Parameter		Segment 1	Segment 2	Segment 3	Segment 4
Incidence of response		31/39 = 79 %	26/33 = 79 %	34/44 = 77 %	32/44 = 73 %
Change of motility pattern %		19	10	29	25
Tonus	increase %	55	30	3	0
	unchanged %	29	35	18	47
	decrease %	16	35	79	53
Frequency	increase %	26	3	0	0
	unchanged %	32	35	50	47
	decrease %	42	62	50	53
Amplitude	increase %	3	4	9	3
	unchanged %	13	31	32	22
	decrease %	84	65	59	75
Amplitude max	increase %	52	27	6	0
	unchanged %	6	8	6	13
	decrease %	42	65	88	87

Table II *In vitro Effects of Prostaglandin E_1 Tested on the Longitudinal Musculature of the Fallopian Tubes from 9 Women in the Secretory Phase*

Parameter		Segment 1	Segment 2	Segment 3	Segment 4
Incidence of response		11/16 = 69 %	21/25 = 84 %	21/24 ≈ 88 %	15/25 ≈ 60 %
Change of motility pattern		0	21	19	20
Tonus	increase %	100	36	5	0
	unchanged %	0	32	24	40
	decrease %	0	32	71	60
Frequency	increase %	27	5	14	13
	unchanged %	73	32	53	67
	decrease %	0	63	33	20
Amplitude	increase %	18	0	14	6
	unchanged %	44	37	33	47
	decrease %	18	63	53	47
Amplitude max	increase %	100	37	5	0
	unchanged %	0	16	10	27
	decrease %	0	47	85	73

and the reverse effect on the rest of the tube and the uterus No difference in response to PGE_1 of tubes examined at different stages of the menstrual cycle is observed On the uterus the inhibitory effect is somewhat more pronounced in the proliferatory phase

The specific action on the proximal part of the tube (segment 1) described for PGE_1 *is also found for* PGE_2 However, for the latter substance, this effect is most pronounced in the secretory phase *The relaxing effect on the rest of the tube is of the same* order for both PGE_1 and PGE_2

The specific effect of PGE_1 and PGE_2 on the proximal part of the tube (segment 1) is lacking for PGE_3 This substance has an inhibitory effect throughout the Fallopian tube

Horton and Main (1963) in experiments on rabbits *in vivo* demonstrated a relaxing effect of PGE_1, PGE_2 and PGE_3 on the Fallopian tube, PGE_2 being equiactive with PGE_1 and PGE_3 being about half as active

On the uterus all three substances exert the same general effect, i e an inhibitory action on both the corpus and the isthmus, the latter part being the most sensitive throughout The relaxing effect of PGE_1, PGE_2 and PGE_3 on the human uterus *in vitro*, described in this paper, is in accordance with the findings of Bygdeman and Eliasson (1963) PGE_3 has a weaker action on the corpus than PGE_1 and PGE_2 the only demonstrable difference between these substances being in their action on the uterus *The incidence of response calculated on all experiments (proli*feratory+secretory phases) with PGE_1 ,PGE_2 and PGE_3 on human uterus are the following $PGE_1=78\%$, $PGE_2=62\%$ and $PGE_3=37\%$ Analogous results as regards the sensitivity of the rat uterus towards PGE_1, PGE_2 and PGE_3 have recently been published (Horton and Main, 1963)

A prostaglandin preparation purified according to Eliasson 1959 containing PGE_1 PGE_2 and PGE_3 has been tested *in vitro* with the same technique (Sandberg *et al* 1963 a) as in the present investigation The results obtained agree with the effects of PGE_1 and PGE_2

Table I *In vitro Effects of Prostaglandin E_1 Tested on the Longitudinal Muscula ture of the Fallopian Tubes from 16 Women in the Proliferatory Phase*

Parameter		Segment 1	Segment 2	Segment 3	Segment 4
Incidence of response		31/39 = 79 %	26/33 = 79 %	34/44 = 77 %	32/44 = 73 %
Change of motility pattern %		19	19	29	25
Tonus	increase %	55	30	3	0
	unchanged %	29	35	18	47
	decrease %	16	35	79	53
Fre quency	increase %	26	3	0	0
	unchanged %	32	35	50	47
	decrease %	42	62	50	53
Ampli tude	increase %	3	4	9	3
	unchanged %	13	31	32	22
	decrease %	84	65	59	75
Ampli tude max	increase %	52	27	6	0
	unchanged %	6	8	6	13
	decrease %	42	65	88	87

Table II *In vitro Effects of Prostaglandin E_2 Tested on the Longitudinal Muscula ture of the Fallopian Tubes from 9 Women in the Secretory Phase*

Parameter		Segment 1	Segment 2	Segment 3	Segment
Incidence of response		11/16 = 69 %	21/25 = 84 %	21/24 = 88 %	15/25 = 60 %
Change of motility pattern		0	21	19	20
Tonus	increase %	100	36	5	0
	unchanged %	0	32	24	40
	decrease %	0	32	71	60
Fre quency	increase %	27	5	14	13
	unchanged %	73	32	53	67
	decrease %	0	63	33	20
Ampli tude	increase %	18	0	14	6
	unchanged %	44	37	33	47
	decrease %	18	63	53	47
Ampli tude max	increase %	100	37	5	0
	unchanged %	0	16	10	27
	decrease %				

Table III *In vitro Effects of Prostaglandin E_2 Tested on Musculature of Corpus and Isthmus from 22 Women in Fertile Age*

Parameter		Nonpregnant uterus			
		Corpus		Isthmus	
		Prolif	Secr	Prolif	Secr
Incidence of response		8/20 = 40 %	40/57 = 70 %	38/41 = 93 %	24/27 = 89 %
Change of motility pattern %		0	23	18	71
Tonus	increase %	0	7	0	0
	unchanged %	25	35	42	58
	decrease %	75	58	58	42
Frequency	increase %	0	0	0	0
	unchanged %	63	42	16	4
	decrease %	37	58	84	96
Amplitude	increase %	0	5	3	0
	unchanged %	50	32	21	8
	decrease %	50	63	76	92
Ampl max	increase %	0	7	0	0
	unchanged %	0	3	5	0
	decrease %	100	90	95	100

Table IV *In vitro Effects of Prostaglandin E_2 Tested on the Longitudinal Musculature of the Fallopian Tubes from 10 Women in the Proliferatory Phase*

Parameter		Segment 1	Segment 2	Segment 3	Segment 4
Incidence of response		19/26 = 73 %	14/20 = 70 %	22/30 = 74 %	19/32 = 60 %
Change of motility pattern %		21	36	9	21
Tonus	increase %	5	0	0	0
	unchanged %	37	64	23	21
	decrease %	58	36	77	79
Frequency	increase %	21	7	4	0
	unchanged %	47	29	64	32
	decrease %	32	64	32	68
Amplitude	increase %	5	0	9	5
	unchanged %	26	29	50	32
	decrease %	69	71	41	63
Amplitude max	increase %	11	0	0	0
	unchanged %	5	21	9	16
	decrease %	84	79	91	84

Table V *In vitro Effects of Prostaglandin E_2 Tested on the Longitudinal Musculature of the Fallopian Tubes from 6 Women in the Secretory Phase*

Parameter		Segment 1	Segment 2	Segment 3	Segment 4
Incidence of response		11/14 79 =	12/16 = 75 %	16/20 = 80 %	13/20 = 65 %
Change of motility pattern %		36	67	6	0
Tonus	increase %	10	0	0	0
	unchanged %	45	42	31	38
	decrease %	45	58	69	62
Frequency	increase %	0	33	19	8
	unchanged %	36	25	44	54
	decrease %	64	42	37	38
Amplitude	increase %	18	0	19	8
	unchanged %	55	17	31	23
	decrease %	27	83	50	69
Amplitude max	increase %	18	0	6	8
	unchanged %	18	0	6	0
	decrease %	64	100	88	92

Table VI *In vitro Effects of Prostaglandin E_2 Tested on Musculature of Corpus and Isthmus from 16 Women of Fertile Age*

Parameter		Nonpregnant uterus			
		Corpus		Isthmus	
		Prolif	Secr	Prolif	Secr
Incidence of response		17 58 29 %	15/29 = 52 %	31/41 = 83 %	20/21 = 95 %
Change of motility pattern		12	27	29	60
Tonus	increase %	0	0	0	0
	unchanged %	77	53	94	85
	decrease %	23	47	6	15
Frequency	increase %	0	0	0	0
	unchanged %	35	20	3	15
	decrease %	65	80	97	85
Amplitude	increase %	6	7	3	0
	unchanged %	12	13	44	15
	decrease %	82	80	53	85
Ampli…	increase %				

SUMMARY

Using Magnus Kehrer's technique the effect of prostaglandin E_2 and E_3 has been investigated on different parts of human Fallopian tube from 41 women, and on corpus and isthmus of the uterus from 38 women in fertile age

Prostaglandin E_2 exerts a specific action as demonstrated by an increase in tonus and amplitude maximum on the proximal part of the tube and an inhibitory action on the rest of the organ and on the uterus

Prostaglandin E_3 produces an inhibitory effect throughout the Fallopian tube as well as on the uterus

The effects of PGE_2 and PGE_3 are discussed in relation to those of PGE_1

Acknowledgments

We are indebted to Professor Sune Bergstrom and Associate Professor Bengt Samuelsson, Dept of Chemistry, Karolinska Institutet, Stockholm, for the kind supply of prostaglandin E_2 and E_3, and to Miss Laila Gustafsson for skilful technical assistance This work was supported by the Swedish Medical Research Council (Project No W 165 and U 161)

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Fylling Petter Acta obst. et gynec. scandinav 43, 103, 1964
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PLASMA OXYTOCINASE ACTIVITY FOLLOWING A SINGLE INJECTION OF PITOCIN

BY

PETTER FYLLING

The ability of oxytocinase to inactivate oxytocin has been demonstrated by many investigators (Werle *et al*, 1941 Page, 1946 Werle and Semm, 1956 Tuppy and Nesvadba 1957 Caldeyro Barcia and Poseiro, 1959 Hartburg Müller, 1960 Titus *et al*, 1960 Centario *et al*, 1961) Sawyer (1954) observed that the capacity of the rat uterus to inactivate oxytocin increases during gestation, but is low at term, possibly because oxytocinase protects the uterus against circulating oxy tocin However most other investigators have not found a de crease in serum or plasma oxytocinase at the end of human preg nancy but rather the opposite Still there are some observations suggesting that oxytocinase represents one of nature s measures for keeping the uterus at rest during pregnancy

It has been shown that when oxytocin is infused for several hours the plasma oxytocinase activity increases (Caldeyro-Barcia and Poseiro 1961 Mendez Bauer 1961, Tuppy, 1961) Such an observation need not necessarily mean that formation of oxytocinase has been stimulated, but could indicate increased release rather than increased formation

In an attempt to elucidate this problem, the work here pre sented deals with the effect of a single intravenous injection of oxytocin on plasma oxytocinase activity in pregnant women

SUMMARY

Using Magnus Kehrer's technique the effect of prostaglandin E_2 and E_3 has been investigated on different parts of human Fallopian tube from 41 women, and on corpus and isthmus of the uterus from 38 women in fertile age

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In an attempt to elucidate this problem, the work here presented deals with the effect of a single intravenous injection of oxytocin on plasma oxytocinase activity in pregnant women

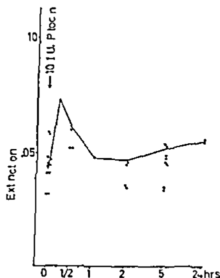


Fig 1 The individual readings are plotted on the scattergram and the line represents the mean values

Material and Methods

The series consisted of 20 pregnant women, from 17 to 42 years old with a gestational stage of 8 to 20 weeks

Ten I U (1 ml) of Pitocin (Parke, Davis & Co) was injected intravenously Blood samples were obtained after 1/4, 1/2, 1, 2, 5, and 24 hours, in a manner described previously (Fylling, 1963) *All samples from individual cases were tested simultaneously in* order to reduce methodical errors Duplicate measurements of enzyme activity were carried out according to the colorimetric method of Klimek and Pietrzycka (1961), the colour densities being measured in Beckman Spectrophotometer, D U at 565 μ

Results and Discussion

As seen in the scattergram (Fig 1) there was some individual variation in the oxytocinase activity, but the differences between extinction readings did not exceed 058 in corresponding measurements

In each of the first samples obtained after the injection the oxytocinase activity was significantly higher than in the control

samples After half an hour the activity tapered off and returned to the original value after 1 hour However, in samples taken after 5 hours the values tended to increase again and continued to increase up to the last samples (24 hours)

The results indicate that following a single injection of Pitocin, the uterus in some way or another releases some of the preformed enzyme into the circulation, whereafter a slightly increased oxytocinase activity is found Both the early and late increases obtained in this series are statistically significant ($P < 001$)

The present results suggest that oxytocinase is one of nature s protective measures for keeping the uterus at rest during pregnancy

SUMMARY

1 The effect of a single injection of Pitocin on the plasma oxytocinase activity is studied in 20 pregnant women

2 The results indicate that following a single injection of Pitocin, the uterus in some way or another releases some of the preformed enzyme into the circulation, and later a slight increased formation is found

Acknowledgement

I am grateful to K Hoftun Knutsen, M D (Head of the Department of Obstetrics and Gynæcology) for his cooperation which was essential to this investigation

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Klinge E., Penttilä, O., and Tissari, A., Acta obst et gynec scandinav 43, 107 1964

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THE CONTENT OF 5 HYDROXYTRYPTAMINE IN HUMAN UTERINE AND PLACENTAL TISSUE, AND THEIR 5 HYDROXYTRYPTOPHAN DECARBOXYLASE AND MONOAMINE OXIDASE ACTIVITIES IN NORMAL AND TOXÆMIC PREGNANCIES

BY

E. KLINGE O PENTTILÄ AND A. TISSARI

Introduction

The clinical picture of toxæmia has led it to be regarded as possible that biologically active amines play a part in the pathogenesis of the toxæmic syndrome Thus it has been attempted to elucidate the possible participation of 5-hydroxytryptamine (5HT) as an ætiological factor in toxæmia by estimating the amine in question and its metabolites in the blood and urine In this study the 5HT content in the uterus and placenta of normal and toxæmic patients have been compared We have also tried to assess if there are in the same tissues any differences between the activities of 5 hydroxytryptophan decarboxylase (5HTPD) and monoamine oxidase (MAO) in toxæmic and normal cases using 5 hydroxytryptamine as the substrate in assessing the MAO activity

Methods

Collection of Material

The following criteria were adopted for the diagnosis of toxæmia

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Received on Febr 22nd, 1964

Table I *The Mean Content in ng/g of 5HT in Human Placenta and Uterus in Normal and Toxæmic Pregnancies Number of Cases in Parentheses*

Specimen	Normal	Toxæmia
Uterus	10 (7)	7 (8)
Placenta	8 (7)	6 (8)

extraction (Tissari, 1963) In addition, enzyme incubations were prepared in wich iproniazid[1] 10^{-3}M was used as MAO inhibitor In these samples the metabolism of 5HT was totally prevented

Results

The contents of uterine and placental 5HT were estimated in eight toxæmic patients and seven control patients Very low contents were found in all samples with no difference between the normal and the toxæmic groups (Table I) There was no significant variation with regard to the parity of the patients

The activity of 5HTPD was studied in a series of six toxæmic and six control pregnancies There was practically no observed activity in either uterine or placental tissue There was a wide variation in the results obtained both in toxæmic and control cases and the differences between the two groups are not significant (Table II) Parity had no effect on the 5HTPD activity

The MAO activities estimated from a group of seven cases are shown in table III The mean values and their SD are calculated in respect of only six severe toxæmic cases the clinical findings of which appear in table IV Particularly high MAO activity was demonstrated in the placental tissue in these cases The results in

Table II *5HTP decarboxylase Activity in Uterine and Placental Tissue in Normal and Toxæmic Pregnancies The Amount of 5HT in ng/g ± SD Formed from 5HTP by 1 g of Tissue/h Number of Cases in Parentheses*

Specimen	Normal	Toxæmia
Uterus	43 ± 36 (6)	29 ± 13 (6)
Placenta	22 ± 13 (6)	20 ± 7 (6)

[1] We are greatly indebted to F Hoffmann La Roche & Co (Basle) for a sample of iproniazid

1. Blood pressure 140/105 or more.
2. Albuminuria exceeding 0.5 G/day and/or weight increase exceeding 15 kg.

Patients who had received Rauwolfia alkaloids during pregnancy were excluded from the series. Cæsarean section was performed under pentobarbital-nitrous oxide-oxygen anæsthesia. Specimens were taken from the uterus and placenta during operation. The uterine sample was taken from the edge of the transverse cervical incision, to ensure that it contained chiefly myometrium. The placental specimen was taken from macroscopically healthy parenchyma. Extraction was carried out as quickly as possible, usually within two hours. Occasionally (particularly when ascertaining enzymatic action) the specimens were frozen (—20° C). It was found that, stored in this way, the tissues remained enzymatically active. Control samples were taken from normal cases matched for age and parity. When storage of tissue was necessary, toxæmic and control samples were again matched as closely as possible.

5HT. The acetone-heptane method (Kärki *et al.*, 1959) was used in the extraction of 5HT. The content of 5HT was estimated biologically by the rat stomach technique (Vane, 1957). Recovery by this method was 75 per cent or more. The results presented in the present study are uncorrected with respect to the amounts recovered. Contractions in the preparates caused by the test specimens were fully prevented by lysergic acid diethylamide.

5HTP-decarboxylase. Enzyme action was studied by determining biologically the 5HT formed from DL-5HTP incubated with the tissue homogenate. West's (1957) modified method was adapted by Tissari (1963) for the analysis of the tissues under consideration. The activity of these incubats was completely abolished after treatment the stomach preparation as previously.

Monoamine oxidase. The method of Bogdanski *et al.* (1957) for estimating MAO was adapted to the analysis of the uterine and placental tissues and the reduction of 5HT was measuerd after incubation. The amount of tissue was so selected that during incubation the placental tissue metabolized about 2/3rds of the substrate and the uterine tissue about 1/10th. The 5HT was again determined biologically from the incubation mixture without

in the excretion of 5HIAA during normal pregnancy The same observation has been made concerning the last six weeks of pregnancy by Kuss and Jaeger (1962) On the other hand, according to van den Driessche and Delhaye (1963) excretion remains relatively constant The latter concept is also supported by Israel *et al* (1959) and by the observations of Crisp and Boutselis (1961) during late pregnancy

As is well known, the 5HT content of the human placenta and uterus is small Earlier, Israel *et al* studied the 5HT content in samples of uterus obtained of a Cæsarean section material from normal gravidas They observed a mean value of 0 03—0 04 μg/g Inoue (1956) made a similar observation regarding the placenta In the present study the values in the normally gravid uterus and placenta (0 01 μg/g) compare approximately with the results obtained by earlier investigators It has not been possible to demonstrate any divergency in the case of toxæmic patients (Table I)

The vasoconstrictive action of 5HT on the blood vessels of the umbilical cord and those of the placenta *in vitro* is ten times greater than that of adrenaline (Åstrom and Samelius, 1957 Gautieri and Ciuchta, 1961) Luschinsky and Singher (1948) have shown that MAO activity in the human placenta is high According to the findings of Brzezinski *et al* (1962) MAO activity in the amniotic fluid in humans is also high During pregnancy there is no MAO activity in blood (Werle and Pechman 1948) The same re earchers have put forward the view that the high activity of MAO in the placenta and amniotic fluid helps to prevent damage to the fœtus by vasoconstrictive amines

It is well known that MAO activity is sensitive to hypoxia (Kohn 1937 Thompson and Tickner 1949) On this basis it is regarded as possible that as a result of a decrease in MAO activity caused by placental ischæmia pressor amines are incompletely inactivated a circumstance that may have significance in the pathogenesis or the progression of toxæmia (Luschinsky 1950) On the other hand it is established that infarcts are often present in toxæmic placentæ It is thought that toxic vasoconstrictor polypeptides are released into the mother s blood stream from these infarcted areas (Berger *et al* 1962)

Table III *MAO-activity in Uterine and Placental Tissues in Normal and Toxæmic Pregnancies The Amount of 5HT in mg/g ± SD Metabolized by 1 g of Tissue The Number of Cases in Parentheses*

Specimen	Normal	Toxæmia
Uterus	0 179 ± 0 074 (7)	0 218 ± 0 164 (7)
Placenta	10 157 ± 1 650 (7)	9 445 ± 2 688 (6)

the toxæmic and control groups did not differ statistically MAO activity in the uterine tissue was very low in both toxæmic and control groups There were no significant variations with parity

Discussion

The excretion of 5HIAA has been used by various workers as an index of 5HT metabolism but the results obtained in toxæmic and normal pregnancies have been contradictory Pokorny and Schmidt (1962) observed periodical fluctuations in the excretion during normal pregnancy and marked rise in the excretion during the second stage of labour They also observed a rise in pregnant hypertensive patients According to the same investigators, the excretion of 5HIAA is slightly raised in toxæmic patients but there is no marked difference as compared with normal pregnancies Carter *et al* (1962) emphasize the considerable fluctuation

Table IV *Details of the Toxæmic Patients Placental MAO Activity in Case Number VII is not Included to the Mean ± SD Presented in Table III The Corresponding Mean ± SD in Per Cent of 5HT Metabolised by the Control Group was 72 1 ± 11 7*

Patient	Diagnosis	Blood Pressure	Albuminuria g day	Amount of 5HT Metabolized by Placenta in Per Cent
I	Toxæmia	170 110	0 5	68 2
II	»	180 130	1 0	51 0
III	»	170 120	0 5	54 3
IV	Pre-eclampsia	190 120	opal	76 2
V	Toxæmia	170 110	0 5	59 0
VI	Pre-eclampsia	150/105	1 0	64 0
VII	Toxæmia Diabetes mellitus	155/100	opal	55 6

with the conception that the forming of pressor amines in the placenta is not an active factor The placenta contains neither noradrenaline nor adrenaline (v Euler, 1945) The lacking decarboxylase activity applies also to the uterine tissue On the basis of the present study no conclusions can be drawn concerning the situation elsewhere in the body Some kind of indication of the factor causing hypertension in animals with experimental placental ischæmia is provided in the observations of Berger and Cavanagh according to which the cause is extra renal

On the basis of the observations made it has not been possible to show that 5HT has any ætiological significance in the toxæmic syndrome

SUMMARY

1 The 5HT content was estimated biologically in specimens of human placenta and uterus obtained at Cæsarean section in normal and toxæmic patients No differences were observed between the different groups

2 The same specimens were examined for monoamine oxidase and 5 hydroxytryptophan decarboxylase activities No statistically significant difference in enzyme activity was observed between the groups examined MAO activity in the normal placenta was very high (10 157 $\pm$ 1 659 milligram of 5HT metabolized by 1 gram of tissue per hour) That of uterine tissue was clearly of lower level (0 179 $\pm$ 0 074 mg/g/h) 5HTPD activity was observed neither in placental nor uterine tissue

3 Results obtained are discussed in relation to the observations of other workers Conclusion is that it has not been possible to show for 5HT any ætiological significance in the toxæmic syndrome

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Interesting, too, is the investigation of Berger and Cavanagh (1963), in which they observed a rise in the blood *pressure of a* rabbit in which placental ischaemia had been experimentally induced Through *the medium of a blood change they also produced* hypertension in non-gravid rabbits However, they gave no closer *definition in their study of the type of agent producing the elevat*ed blood pressure

Sandler and Coveney (1962) differ from Luschinsky, having come to the conclusion that placental MAO activity is reduced in toxæmia In their opinion this reduced activity is related to the severity of the toxæmia In assessing MAO activity they used, like Luschinsky, a gasometric method, with tyramine as the substrate In the present study, 5HT was used as the substrate and, as is clear from table III, it was not possible to confirm the results of Sandler *et al in the comparison* between normal and toxæmic patients Sandler and Baldock (1963) were *unable to prove conclusively any common lessening of MAO* activity in toxæmia If a common diminution of MAO activity is a factor in the pathogenesis of toxæmia, it would follow that the administering of a MAO-inhibitor to pregnant women would induce toxæmia Observations do not support this conception (Dally, personal communication to Sandler and Coveney, 1962) One would expect that a common decrease in MAO activity in toxæmia would result in increased excretion of 5HT or its O-conjugates in the urine Burn (1953) was unable to record any increase in the catecholamine content of the plasma or urine of toxæmic patients However, Castren (1963) succeeded in showing that manual workers of a mild stage of toxæmia excreted an elevated quantity of catecholamines, even though this remained within normal limits compared with normal gravidas

Page (1945) was unable to demonstrate any dihydroxyphenylalanine (DOPA) decarboxylase activity in the placenta of either normal or toxæmic cases The low values of this study are in *agreement with those of Page and Thompson (1950)* In this investigation 5HTP was used as the substrate According to *Westermann (1958) both DOPA and 5HTP are decarboxylated* by the same enzyme In general, the presence of this decarboxylase is *proprotional to that of 5HT These findings are in keeping*

Cordey René and Stander Richard W., Acta obst. et gynec. scandinav 43 115 1964

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ESTIMATION OF INTRAUTERINE PRESSURE BY AN EXTERNAL TRANSDUCER

BY

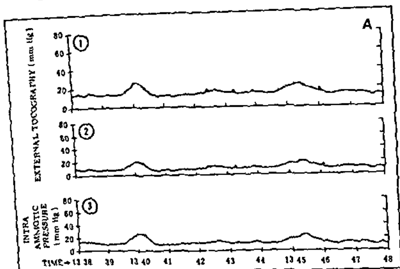
RENÉ CORDEY M. D AND RICHARD W STANDER M.D[1]

In 1957 Malmstrom described an external transducer and ascribed to it the capability of measuring intrauterine pressure in human pregnant patients by application to the abdominal wall The basic unit consists of a hollow transducer through which a constant flow of oxygen or compressed air is maintained The transducer is affixed to the abdominal wall by means of a belt encircling the patient. The tension converts the anterior abdominal wall and uterine wall immediately beneath the transducer to a plane surface The sensitive portion of the transducer is a thin rubber diaphragm As intrauterine pressure rises slight elevation of the diaphragm prevents escape of gas from the transducer, and pressure in the latter rises until it reaches equilibrium with intrauterine pressure Fig 1 indicates the basic design of the transducer For the purpose of making permanent records on a continuous basis the original pressure gauge method of measuring pressure in the external transducer has since been replaced by a simple Grafax ink writing recording unit Modifications of the transducer s physical characteristics have also been made

[1] Faciliti s provided by Cardiovascular Clinical Research Grant H-6308 National Heart Institute and supported in part by the Indiana Heart Association.

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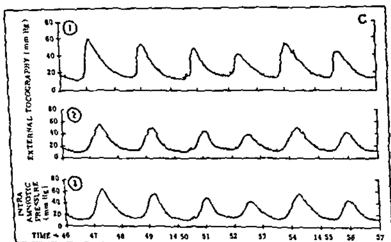


Fig 2 Thirty three year old g 4 p 3 with history of Rh sensitization — A Thirty nine weeks gestation. Spontaneous uterine motility as recorded by external transducer (1 and 2) and direct intrauterine pressure (3) Small pressure variations are well recorded by the external transducer — C Increase in intensity and frequency of uterine contractions resulting from intravenous infusion of dilute oxytocin Pressures from the external transducer follow larger variations in intrauterine pressure

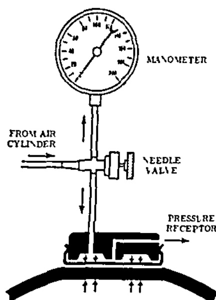


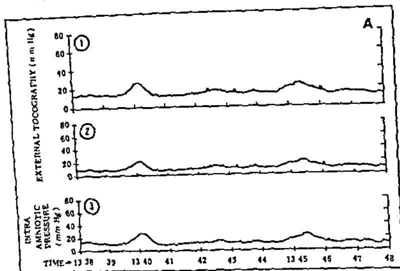
Fig 1 *Schematic representation of the Malmstrom transducer*

One of us (R C) has reported on the value of the recordings made by the external transducer in demonstrating abnormal labour patterns, as an aid in the control of intravenous oxytocin infusion and in performance of oxytocin sensitivity tests (Cordey, 1962) In addition, this method of external recording has been utilized in determining response of the human gravid uterus to drugs administered to the mother (Cordey, 1964)

Doubts are always expressed concerning the ability of any external sensing device to measure intrauterine pressure with reliability The opportunity arose to study the performance of the external transducer of Malmstrom in conjunction with direct intrauterine pressure measurement after the method of Alvarez and Caldeyro-Barcia (1950)

Materials and Methods

Three patients at or near term formed the basis for the comparative study Two of the patients were at 38 weeks gestation and the third at 40 weeks, as judged by their menstrual histories None was in labour or had ruptured membranes at the onset of



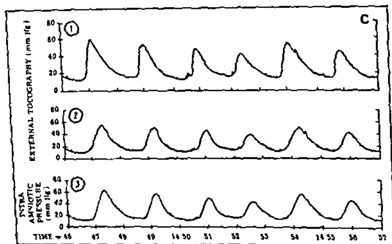
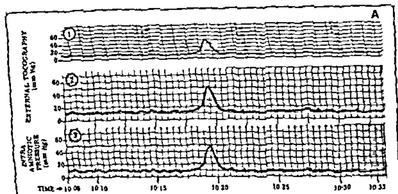


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monitoring One patient (394) exhibited mild evidence of Rh sensitization and for this reason had been admitted for induction of labour The other 2 patients (396 and 397) were selected for demonstration purposes After flow of gas had been established through the external transducer system, a connection was made to a Statham 23 BB transducer and strain gauge coupler to an Offner Dynograph R recording system Since the normal flow of gas through the transducer produces a positive pressure of 6–8 mm Hg, the self-contained recorder and Offner recorder were adjusted to zero value before application of the transducer to the anterior abdominal wall After the transducer was secured in the operating position, a positive pressure was again recorded, reflecting intrauterine pressure Transabdominal amniocentesis was then accomplished under local anæsthesia after surgical preparation of the abdomen A polyethylene catheter was placed within the amnion and this was in turn connected to a second Statham 23 BB pressure transducer and this system was filled with physiologic saline This pressure was recorded on another channel of the Offner recorder The zero recording of this system was established hydrostatically at the level of the anterior abdominal wall with the patient in the supine position Thus, one record of external transducer pressure was obtained on the small recorder supplied with the system, while the same pressure was recorded simultaneously with fluid pressure directly from the amniotic cavity on another recording system Patients remained supine throughout the procedure and a total of 6 hours of simultaneous recordings was made

Results

Figs 2, 3 and 4 are photographs of simultaneous recordings of pressure in the external transducer and pressure recorded directly from the amniotic cavity In each figure, recording no 1 is external transducer pressure recorded on the curvilinear Grafax recorder No 2 is external transducer pressure recorded on the rectilinear Offner recorder No 3 is a direct recording of intrauterine pressure via the transabdominal intrauterine catheter



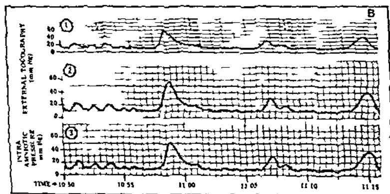
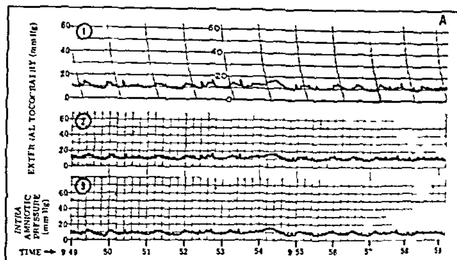


Fig 3 Thirty-five year old g 12 p 0 Thirty-eight weeks gestation Moderate *hydramnios* – A Spontaneous uterine contractility as measured by external transducer pressure (1 and 2) and intrauterine catheter (3) – B A moderate increase in uterine contractility is noted in both recording parameters 15 *min* u es after the intravenous administration of 75 mg dextropropoxyphene HCl



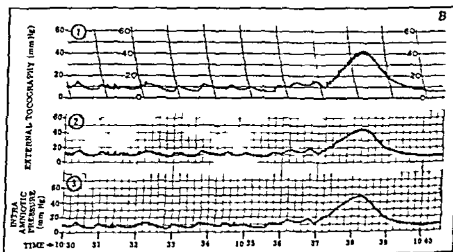


Fig 4 Thirty two year old, g 3 p 2 Thirty-eight weeks gestation, Breech presentation – A. *Spontaneous uterine activity* Note the sensitivity of the external recordings (1 and 2) – B Uterine activity 15 minutes after intramuscular administration of 150 mg of sparteine sulphate Maternal respirations are somewhat more pronounced in pressures recorded from the external transducer

Fig 2 indicates spontaneous uterine motility as well as that induced by intravenous infusion of a dilute solution of oxytocin while Figs 3 and 4 demonstrate the uterine response to dextro propoxyphene hydrochloride and sparteine sulphate

SUMMARY

No external transducer yet designed has the ability to measure intrauterine pressure exactly Differences of a few mm Hg exist between external transducer pressure and true intrauterine pres sure even under ideal circumstances because of the physical properties of intervening maternal tissues However, comparative recordings indicate that this particular transducer is capable of reproducing a variety of wave forms resulting from changes in intrauterine pressure In addition, it provides a sufficiently ac- curate estimation of intrauterine pressure to warrant a variety of applications It should prove beneficial as an educational device in clinical teaching as well as a useful tool in clinical research

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ENCIRCLING SUTURE OF THE CERVIX IN PLACENTA PRÆVIA

BY

BO von FRIESEN

Since 1950, Lovset (1959) working in Norway, has applied an encircling suture to the cervix in cases of placenta prævia This has been found to prevent further bleeding until such time as labour commences Lovset's results have continued to be favourable (Lovset, 1963) His patients are allowed to leave hospital providing that they do not live too far away and they are instructed to return at once in the event of bleeding or pains

The present writer has used the method since 1960, but otherwise it does not seem to have spread to other clinics in Sweden Nor has any other mention of the method been found in the literature This may be because Lovset did not publish any detailed results, but only his general impressions Since our own impressions are favourable, it was thought justifiable to publish an account of the patients seen and treated in this way at Lidköping notwithstanding that they are relatively few in number

Technique

Lovset (1959) described the method as follows

"Initially a circular suture was applied in the fornices going through the vaginal mucosa and into the uterine muscle at each stitch, 5—6 bites being taken in all The stitches were put as high up in the fornices as possible without doing any dissection and

when the suture had encompassed the whole periphery it was tightened sufficiently to moor the lower uterine segment and prevent the internal part of the cervix from dilating until labour pains started At first we used silk as suture material but we now prefer braided nylon '

The present writer uses thick Mersilene (Ethicon[R],) a braided synthetic material which is easy to handle The knots should preferably be tied in the anterior fornix and the ends left 2—3 cm long so that they are easy to find when the time comes to remove them

Anæsthesia

General anæsthesia together with a muscle relaxant is recommended This makes the procedure even simpler and helps to prevent the onset of contractions

Diagnosis

In doubtful cases pelvic arteriography is recommended (Fernstrom 1955 Borell *et al* 1963) The dosage of irradiation is lower (0 3 r per plate) than for soft tissue X rays The fœtal gonads are invariably outside the field of radiation in instances of cephalic presentation which also applies to the maternal ovaries in many cases and which is important accurate information is obtained even in early cases

In 3 of our 7 cases the first hæmorrhage occurred before the 28th week of pregnancy that is to say so early that the diagnosis could hardly be reached by any other means than pelvic arteriography

Samuelsson and Sjovall (1957) recommended that a hair pin or hair dressing clip be fastened to one or other lip of the cervix before performing placentography the distance between the cervix and the lower limit of the placenta can thereby be accurately determined and this in turn may dictate the choice of method for delivery

Sjovall (1964) favours the use of a ring forceps for this purpose

During the four year period Feb 1st 1960—Jan 31st 1964 placenta prævia was recorded in 18 out of 4500 deliveries (0 4

per cent) Westgren (1954) quotes 0 26 per cent for two large Swedish series and Nieminen *et al* (1964) 0 57 per cent for a large Finnish series The diagnosis "lateral placenta prævia" is often subjective and this may account for the discrepancies

Of the 18 cases, eight were classified as complete placenta prævia which is to say that the placenta covered the entire internal cervical os The remaining 10 belonged to a group referred to as incomplete placenta prævia

Suture of the cervix was performed in 7 cases, five with complete and two with incomplete placenta prævia The following are short accounts of the treated cases

Case 1 Age—30 years one previous delivery Moderate bleeding in 31st week of pregnancy—no labour pains Pelvic arteriography "placenta situated in pelvis" Suture of cervix performed at 34th week patient discharged on tenth day During 39th week slight menstruation like bleeding—no pains Cæsarean section performed two days later The placenta was found to be lying centrally over the internal os No old blood clot was found in the uterus Healthy male child weighing 3550 g

Case 2 Age—33 years two previous deliveries Moderate bleeding with slight lower back pains in 26th week imminent abortion Recurrence of bleeding and pains during 33rd week Soft tissue X-rays suggest abnormally low placenta Suture of cervix performed patient discharged after three days After a further five days, slight pains still present but no bleeding Cæsarean section performed (during 33rd week) placenta found to cover the internal os completely Healthy female child weighing 2220 g

Case 3 Age—42 years six previous deliveries Slight bleeding during 30th week Pelvic arteriography "low placenta" Suture of cervix patient discharged after three days Onset of labour pains at 40th week Head well engaged Suture removed from cervix normal delivery Healthy female child weighing 3460 g

Case 4 Age—29 years one previous delivery Hæmorrhage during 33rd week consisting of about 15 g clotted blood Soft tissue X rays suggestive of low placenta Twelve hours later—profuse bleeding while lying in bed Suture of cervix performed as rapidly as possible—the patient continuing to bleed briskly the while Since dependable hæmostasis was not secured at first two further sutures were inserted and tied in the lateral fornices Bleeding then ceased Three bottles of blood were given The extra stitches were removed after 2 days and the patient was able to go home on the fourth day Lowest hæmoglobin level 9 4 g per 100 ml Thirteen days after suture of the cervix a slight painless blood loss occurred Slight pains occurred subsequently and increased in intensity, necessitating Cæsarean section (35th week) A posterior placenta covered a region including the internal os and continued anteriorly for 5—10 cm Healthy female child weighing 2560 g

Case 5 Age—37 years four previous deliveries External version performed for breech presentation in 34th week Slight bleeding and pains lasting 24 hours at beginning of 39th week Seen 3 days later for routine check and admitted to hospital because of history of bleeding Soft tissue X ray placenta situated in the intermediate segment on the left side and reaching down into the pelvis head not engaged and somewhat to the right Suture of cervix performed the same day (anæsthesia unsatisfactory) Slight pains and moderate bleeding necessitated Cæsarean section The placenta was on the posterior wall and to the left reaching down to within a few centimetres of the internal os Healthy female child weighing 3340 g

Case 6 Age—29 years no previous deliveries Slight bleeding at 26th week Two further slight bleeds during 28th week Suture of cervix performed Patient discharged two days later Pelvic arteriography at 32nd week placenta below level of fœtal head At 38th week—hæmorrhage approx 300 ml—no labour pains Admitted to hospital 2 hours later—bleeding moderate Immediate Cæsarean section Placenta entirely covering internal os Uterus contained approx 200 ml blood which looked as though it may have been there since before the operation One bottle of blood was given Lowest hæmoglobin level reached—8 5 g per 100 ml Healthy female child weighing 3430 g

Case 7 Age—26 years no previous deliveries Sudden slight bleed at 26th week No pains Isoxsuprin (Duvadilan[R]) by mouth Pelvic arteriography performed one week later "complete placenta prævia Suture of cervix performed same day Discharged from hospital 2 days later Isoxsuprin discontinued At 34th week passed hen s egg sized clot—slight pains later Isoxsuprin by mouth restarted subsequently also by injection Increasing pains despite treatment Scanty bleeding Cæsarean section following day Placenta mainly on posterior wall but reaching forward beyond the internal os as far as the *incision in the* lower uterine segment Healthy female child weighing 2470 g

With one exception these patients were allowed to leave hospital a few days after suture The exception was a patient who began to have contractions in association with a badly administered anæsthetic necessitating delivery later the same day In all except one case treated by encircling suture of the cervix the bleeding first occurred *before the 34th week* of pregnancy If bleeding first occurred during *the 37th week or later* alternative treatment was adopted The time of onset of the bleeding together with the presence or absence of contractions thus decided whether immediate delivery or suture of the cervix *should* be performed In one case however incomplete placenta prævia was an incidental finding at Cæsarean section performed during the 39th week of pregnancy

The interval between encircling suture and delivery was in two cases 10 weeks in one case 7 weeks in one case 5 weeks in one

case 2 weeks, and in two cases less than 2 weeks The appearance of the cervix was in all cases normal both after suture and after delivery **Lovset** (1959) describes cases where the suture was retained for as long as 12 weeks We have used the same suture technique in cases of cervical incompetence and in one of these the suture was retained for 24 weeks without causing any change in the appearance of the cervix

Delivery was by Cæsarean section in 6 cases and was spontaneous in one case after artificial rupture of the membranes In 2 cases the procedure (section or rupture of the membranes) was undertaken electively and was not dictated by the appearance of symptoms Cæsarean section before term was necessitated by contractions in 4 cases and by bleeding in one case

Two of the 11 cases in which suture was not performed had *complete* and 9 *had incomplete* placenta prævia *In addition* to the 2 cases of complete placenta prævia Cæsarean section was also performed *in* 5 *cases of incomplete placenta prævia Three cases of* incomplete placenta prævia were delivered with the Vacuum *Extractor and in one case artificial rupture of the membranes* was followed by spontaneous delivery

Among the cases treated by suture of the cervix the birth weights varied from 2220 g to 3460 g Only 2 infants weighed less than 2500 g In those not so treated the birth-weights varied from 2630 g to 3860 g The perinatal mortality was *nil*

Among the more recent Scandinavian publications concerning placenta prævia may be mentioned the following In **Westgren's** (1954) series of 350 cases collected over the period 1940—1949, 36 per cent of the infants weighed less than 2500 g at birth and the perinatal mortality was at least 36 per cent **Borell** *et al* (1963) gave an account of 47 cases collected over the period 1955—1961 In this series 8 infants died perinatally all weighing less than 2400 g at birth **Nieminen** *et al (1964) reported that in their series of* 420 cases, covering the period 1952—1961, 34 7 per cent of infants had a birth-weight of less than 2500 g The perinatal mortality was 19 7 per cent (or 44 5 per cent in infants weighing less than 2500 g and 6 6 per cent for full term infants)

Discussion

Rest in bed has previously been the only conservative method available in cases of placenta prævia We now regard the encircling suture method as being capable not only of arresting even severe hæmorrhage in the majority of cases of placenta prævia provided that the patient is not having contractions but also as preventing severe hæmorrhage afterwards Our series with its strikingly low incidence of birth weights under 2500 g and an equally low perinatal mortality rate suggests that the method allows pregnancy to proceed nearer to term than is otherwise possible in these cases The patient is furthermore permitted to leave hospital which has obvious advantages for both parties

It seems likely that the encircling suture of the cervix acts by immobilising the isthmus and thus preventing continued separation of the placenta prævia

The procedure is so simple that it can be performed as an emergency measure without waiting for confirmation of the diagnosis If the diagnosis of placenta prævia can later be excluded the suture is removed We have seen 4 such cases

When the acute bleeding has been dealt with the question then arises as to how to prevent the premature onset of labour It is possible that more could be done by ordering complete rest This we have not done A further possibility is the prophylactic and therapeutic use of isoxsuprin for the prevention and suppression, respectively of premature labour Sufficient experience of this method has not yet been gained in cases of placenta prævia however

SUMMARY

Encircling suture of the cervix by the method of Lovset (1959) has been used in 7 cases of placenta prævia of which 5 were complete The method is simple and free from complications Delivery can in some of the cases be postponed in this way until the fœtus has become more mature and serious bleeding can in most cases be stopped or prevented Since we began using this technique four years ago we have been called upon to deal with 18 cases of placenta prævia Not one child was lost A birth-weight of less than 2500 g was recorded on only two occasions

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COMPLICATIONS DURING FIBRINOGEN THERAPY IN A CASE OF ABRUPTIO PLACENTÆ

BY

OLE K ALBRECHTSEN AND PREBEN SKJODT

Opinions are divided concerning the cause of the hypo- or afibrinogenæmia which has been observed following severe cases of abruptio placentæ One theory is that of Schneider (1959) who claims that tissue thromboplastin from the decidua and placenta may enter the circulation and convert the fibrinogen in the blood to fibrin intravascularly This may give rise to so called obstetrical shock if the fibrin is deposited in the pumonary circulation This latter condition is characterized by dyspnœa hypotension and dilatation of the right heart An increase in the fibrinolytic activity of the blood may follow resulting in further increase in the bleeding tendency

The present paper is a report of a case of abruptio placentæ with hypofibrinogenæmia treated with human fibrinogen before delivery This fibrinogen therapy did not have the desired effect On the contrary it further aggravated the patient s condition presumably because of an intravascular conversion of the administered fibrinogen to fibrin

Case Report

Case rec 481/6?-63 A 23 year-old gravida II para I No major illnesses and no family history of hæmorrhagic diathesis No previous bleeding tend

ency, either during pregnancy and labour or when not pregnant Last menstrual period at the end of September 1961 No complications during pregnancy Regular antenatal care by her doctor and midwife No abnor malities had been found

On June 7th, 1962, at 9 45 p m she suddenly felt unwell She complained of pain in the upper abdomen and felt nauseated She fell on the floor in a faint, but rapidly regained consciousness There was profuse uterine bleeding accompanied by severe pain in the back, radiating to the interscapular region The attending physician found a blood pressure of 100/60 and a feeble rapid pulse The patient was admitted to hospital immediately

On admission she was pale, cold, sweating with a blood pressure of 100/55 and a feeble, rapid pulse of 120/min She was complaining of severe, persistent pain in the lower abdomen, radiating to the back The fœtus was in a cephalic presentation Fœtal heart sounds faint, but regular, 116/min There was marked tension of the uterus and slight bleeding from the vagina

Shortly after admission, the B P fell to 70/40 Oxygen was administered a blood sample was taken from an arm vein, and infusion of human serum was started at 11 15 p m, as whole blood was not yet available Her condi tion improved a little, and a vaginal examination was performed The head was found to be mobile at the pelvic inlet The cervix was short and rather tight The orifice admitted only a finger There was slight tension of the membranes which were punctured, evacuating about 1100 ml of hæmor rhagic amniotic fluid Catheterization yielded very blood stained urine Rapid analysis of stabilized venous blood (cf coagulation studies) showed that after addition of thrombin a small clot formed in 13 seconds This clot disappeared after standing at 37° C for 165 minutes Upon addition of bovine fibrinogen and thrombin (corrected thrombin time determination) a solid clot formed in 10 seconds This clot did not dissolve in 24 hours

At midnight, a blood transfusion was started The blood pressure rose to 125/75 and the pulse rate fell to 90/min There were now increasing uterine contractions, but the fœtal heart sounds were no longer audible There was profuse bleeding from the vagina

At 0 55 a m another rapid analysis of stabilized venous blood was carried out This yielded only a very small clot 25 seconds after adding thrombin However, this clot was stable and did not disappear after standing for 24 hours at 37°C in a water bath On corrected thrombin time determination, a solid clot formed in 9 seconds and this clot too had not dissolved in 24 hours Owing to the hypofibrinogenæmia it was decided to administer fibrinogen (6 g dissolved in 300 ml physiological saline)

After a few ml of this solution had been infused, the patient's condition deteriorated Her blood pressure fell the pulse rate rose she had nausea vomiting paræsthesiæ of the fingers, and swelling of the tongue There was no urticarial rash The infusion of fibrinogen was immediately stopped and the symptoms subsided in about 30 minutes

Since bleeding from the vagina was still profuse and it was feared that

the delivery would be complicated by serious hæmorrhage due to the hypofibrinogenæmia infusion of a new batch of fibrinogen was started at 1 35 a m This resulted in an immediate reaction of the same kind as before and the infusion was stopped Repeated infusion of fibrinogen 10 minutes later had the same effect but after this third reaction had subsided the patient tolerated a very slow infusion of a total of 6 g fibrinogen. During the further treatment with blood transfusion oxytocin infusion and pethidine the pains increased but there was still bleeding from the vagina

At 2 50 a m. another determination of the thrombin time and of the corrected thrombin time was done Now a small clot formed in 13 seconds and had disappeared again in 70 minutes when left at 37°C The corrected plasma thrombin time was 10 sec and this solid clot had also disappeared after standing for 70 minutes The treatment was continued by a rapid infusion of a further 6 g fibrinogen which the patient tolerated without side effects and at 3 25 a m she delivered a stillborn boy of 3 040 g The placenta was delivered spontaneously 5 minutes later and at the same time 300 g clots were evacuated The uterus was at that time well contracted but the patient continued to bleed severely

On rapid analysis of venous blood at 4 20 a m a massive clot formed in 12 seconds on addition of thrombin to plasma The corrected plasma thrombin time was 9 seconds None of the clots had dissolved after standing for 24 hours at 37 C The bleeding gradually decreased during continued blood transfusion

At 8 o clock in the morning the patient s condition was satisfactory the blood pressure being stable and the pulse strong and regular

In the course of the next 24 hours the patient passed 1 540 ml bloody urine, but thereafter the urine became clear with a specific gravity of 1010 The further course was uneventful and the patient was feeling well when discharged one week later Her hæmoglobin level on June 12th was 84 %

Coagulation Studies

Venous blood and vaginal blood was collected into tubes (14 × 100 mm) with dried potassium ammonium oxalate (Winthrobe) as anticoagulant The stabilized venous blood was centrifuged at 3500 rpm for 15 minutes Determination of plasma thrombin time was then carried out adding 0 2 ml thrombin Roche (100 NIH/ml) to 0 2 ml plasma Such a thrombin time determination depends upon the fibrinogen content but is also influenced by the possible presence of inhibitors (antithrombin) To correct for a possible deficiency of fibrinogen, the corrected thrombin time was determined in a mixture of 0 2 ml plasma 0 1 ml 0 8 % bovine

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Venous blood and vaginal blood was collected into tubes (14 × 100 mm) with dried potassium ammonium oxalate (Winthrobe) as anticoagulant The stabilized venous blood was centrifuged at 3500 rpm for 15 minutes Determination of plasma thrombin time was then carried out adding 0 2 ml thrombin Roche (100 NIH/ml) to 0 2 ml plasma Such a thrombin time determination depends upon the fibrinogen content but is also influenced by the possible presence of inhibitors (antithrombin) To correct for a possible deficiency of fibrinogen, the corrected thrombin time was determined in a mixture of 0 2 ml plasma, 0 1 ml 0 8 % bovine

fibrinogen (Astrup and Müllertz, 1952) and 0.1 ml thrombin. Normally, clotting will occur in a few seconds. The tubes were left in a water bath at 37° C and observed for fibrinolysis. Normally, there will be no dissolution of the clot in 24 hours.

The remainder of the plasma was stored at -20° C for subsequent analysis of prothrombin time, concentration of factors II and VII (prothrombin-proconvertin), factor V (proaccelerin), factor I (fibrinogen), and thromboplastin generation screening test as described in a previous publication (Albrechtsen and Skjødt, 1962). Moreover, determination of fibrinolytic activity in plasma and in isoelectrically precipitated plasma (Astrup and Rasmussen, 1958) was carried out by the fibrin plate methods (standard fibrin plates (Astrup and Müllertz, 1952) and heated fibrin plates (Lassen, 1952)).

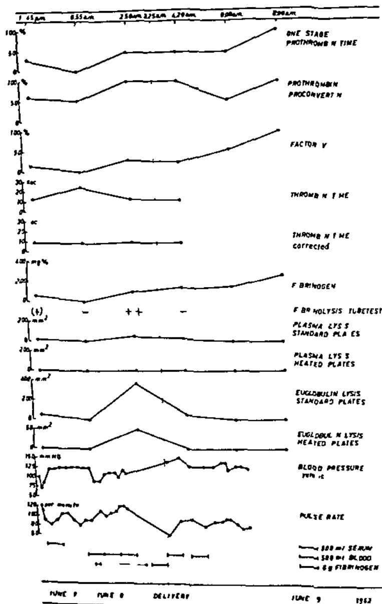
Results

The results of the coagulation studies are given in Fig. 1 which also shows the blood pressure, pulse rate, and the treatment with serum, blood, and fibrinogen.

Shortly after the patient arrived at the hospital, at 11.15 p.m., the prothrombin time was considerably prolonged, the concentration of prothrombin-proconvertin was somewhat reduced, the factor V concentration considerably reduced, the thrombin time slightly prolonged, and the fibrinogen concentration 60 mg/100 ml. The corrected thrombin time was normal, indicating that no antithrombin was present. There was no plasmin activity either in the plasma or in isoelectrically precipitated plasma estimated on heated fibrin plates, and only negligible activity when it was estimated on standard fibrin plates.

After the infusion of 500 ml human serum and blood trans-

Fig. 1. Variations in the concentration of the coagulation factors (Quick prothrombin, proconvertin, factor V, thrombin time, corrected thrombin time, fibrinogen, clot lysis, fibrinolytic activity of untreated plasma on standard and heated fibrin plates and of isoelectrically precipitated plasma on standard and heated fibrin plates) compared with the changes in blood pressure, pulse rate and the treatment instituted.



fusion had been commenced, the coagulation status had further deteriorated (at 0 55 a m) The fibrinogen concentration and the concentration of factor V were decreasing The thrombin time was further prolonged, but could be corrected by adding fibrinogen Thus, there was still no antithrombin At this time there was no fibrinolytic activity in the blood

At 2 50 a m, when the patient had received a total of 1500 c c of blood and 6 g fibrinogen, the coagulation status was somewhat improved, but the fibrinogen concentration, 100 mg/100 ml, was far from the level which ought to be expected after infusion of almost 7 5 g fibrinogen At this time, there was very considerable fibrinolytic activity, on the standard as well as on the heated fibrin plates, indicating the presence of plasminogen activators as well as of plasmin

After another infusion of 6 g fibrinogen and 500 ml blood, at 4 20 a m, 55 minutes after delivery, the fibrinolysis was greatly reduced but the fibrinogen concentration had risen negligibly, to 140 mg/100 ml, a value out of proportion to the approx 14 g of administered fibrinogen

At 8 a m, after a further infusion of 500 ml blood, the fibrinogen concentration was 150 mg/100 ml, the fibrinolysis had subsided, the factor V concentration had increased, and the bleeding had stopped Twenty-four hours later, the coagulation status was normal

The thromboplastin generation screening test by the method of Hicks and Pitney (1957) was carried out as described previously (Albrechtsen and Skjodt, 1962) This test affords information regarding the formation of plasma thromboplastin from the pre stages factor VIII (antihæmophilic globulin A), factor IX (Christmas factor), Hageman factor, plasma thromboplastin antecedent (PTA), etc, as the calcium as well as the platelet factor are present in excess in this special test The results are given in Fig 2 On admission at 11 15 p m the thromboplastin generation was normal During the subsequent approx 3 hours, there was a slightly delayed formation of plasma thromboplastin, but 24 hours after the cessation of bleeding the formation of plasma thromboplastin was again normal

The following results were obtained by analysing vaginal blood

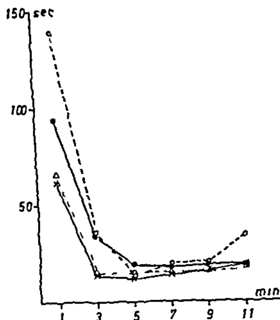


Fig 2 Thromboplastin generation screening test in the peripheral blood on admission and during treatment

Symbols x ———— x at 11 15 p m
● ———— ● at 0 55 a m
○ -------- ○ at 2 50 a m
△ △ at 8 00 a m the next morning

Abscissa Time in minutes
Ordinate Clotting time in seconds

collected immediately after the delivery of the placenta Prothrombin time 0% prothrombin proconvertin 19%, factor V concentration below 1%, fibrinogen concentration 0 mg/100 ml There was no fibrinolytic activity Fig 3 shows the thromboplastin generation in the vaginal blood comparing it with a corresponding analysis of the peripheral blood shortly before delivery These results indicate an increased thromboplastic activity in the vaginal blood as compared with the peripheral blood, but only a very slight formation of plasma thromboplastin

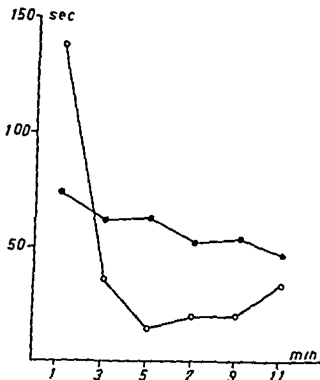


Fig 3 Thromboplastin generation screening test in vaginal blood during delivery and in the peripheral blood shortly before delivery
Symbols ● ———————— ● vaginal blood
○ ———————— ○ peripheral blood
Abscissa and ordinate as in Fig 2

Discussion

Three theories have been advanced in explanation of the hypo- or afibrinogenæmia which may be present following abruptio placentæ

In Schneiders (1959) opinion, tissue thromboplastin passes into the blood stream from the decidua and placenta, causing intravascular coagulation consuming circulating fibrinogen Secondarily, this intravascular coagulation process is supposed to give rise to activation of the fibrinolytic enzyme system of the blood in a manner still unknown

Others, including Phillips (1962), do not accept this view, claiming that activation of fibrinolysis is primary and that the

presence of plasmin in the blood can explain the hæmorrhagic diathesis observed in abruptio placentæ

A third possibility, which has been subjected to detailed studies by several authors (Stouffer and Ashworth, 1958, Nielsen, 1963) is that the hypo or afibrinogenæmia as well as the con sumption of other coagulation components of the blood may primarily be related to the retroplacental coagulation process It has been demonstrated that the fibrin content of the retroplacental hæmatoma found in most mild cases of abruptio is very high and perhaps corresponds to the fibrinogen which has disappeared from the blood stream

The reason why the views are so divergent must be that in many respects fibrinolysis and activation of the coagulation process cause the same changes Moreover, it can hardly be ruled out that the symptom complex in abruptio placentæ may be elicited by a number of mechanisms acting at the same time

In the present case we had a chance of performing coagulation studies at frequent intervals during the course of a severe abruptio placentæ The first blood sample was obtained 90 minutes after the onset of the first symptoms or 250 minutes before delivery

The result of the investigations at 11 15 p m do not permit a definite conclusion as to which of the three mechanisms was operative in the present case The low prothrombin proconvertin, factor V and fibrinogen values might be caused by an active in travascular or retroplacental coagulation process and they might also be caused by pronounced fibrinolysis which have disappeared at the time of admission However, the normal plasma thromboplastin formation at this time is evidence to some extent against an active fibrinolytic process as such a process may cause a breakdown of factor VIII and thereby a delayed plasma thromboplastin formation

As already mentioned the patient went into shock when the symptoms appeared at a time before bleeding from the vagina had started This might possibly indicate an intravascular coagula tion process (obstetrical shock as described by Schneider)

The further decrease in the concentration of factor V and fibrinogen as well as the negligible decrease in the concentration of prothrombin proconvertin between 11 15 p m and 0 55 a m

also indicate an active coagulation process, especially since no fibrinolytic activity could be demonstrated in the blood during this period. However, the investigations do not give any indication as to whether this coagulation process was retroplacental or intravascular.

The merely moderate increase in fibrinogen concentration between 0.55 and 2.50 a.m., despite a slow infusion of considerable amounts of fibrinogen (about 7.5 g) shows that a large part of the infused fibrinogen was consumed. This may be explained either by a fibrinogenolytic process (Beller, Glas and Roemer, 1961) involving breakdown of the fibrinogen, or by conversion of the infused fibrinogen into fibrin.

The marked difference between the fibrinolytic activity in untreated plasma and in isoelectrically precipitated plasma, in which the fibrinolytic inhibitors have been partially removed, shows that at this moment the plasma contained a considerable quantity of such inhibitors. It is not very likely, therefore, that fibrinogenolysis had taken place, as these inhibitors would counteract the direct breakdown of fibrinogen by plasmin.

On the other hand, the exacerbation of the patient's condition during the infusion of fibrinogen might indicate that an intravascular coagulation process had taken place and induced secondary fibrinolysis.

Later (at 2.50 a.m.) fibrinogen could be infused without side effects, but there was no appreciable increase in the fibrinogen concentration during this infusion. It is possible, therefore, that the administered fibrinogen was converted intravascularly to fibrin, but that simultaneously the pronounced fibrinolytic activity resulted in rapid re-dissolution of the fibrin and thereby counteracted the occurrence of the complications which accompanied the first infusion. Owing to the great affinity of plasmin for fibrin, the fibrinolytic inhibitors are unable to inhibit such a process (Müllertz, 1956).

After delivery, at 4.20 a.m., the pronounced fibrinolysis had again disappeared, and in the course of the subsequent 24 hours the coagulation status returned to normal without any active therapy.

It has been demonstrated that the decrease in fibrinogen in

fairly mild cases of abruptio placentæ is due mainly to retroplacental precipitation of fibrin (Stouffer and Ashworth, 1958, Nielsen 1963) Moreover, the significance of fibrinolysis as an ætiological factor in hæmorrhagic disorders following abruptio placentæ has not been fully elucidated Nevertheless, it is still impossible to rule out that intravascular formation of fibrin and a consequent secondary fibrinolysis may be responsible for the clinical manifestations and bleeding tendency in the more severe cases This view is supported by the present findings

Consequently it must be carefully considered whether it is justified to infuse fibrinogen before the termination of delivery, at a time while there is still a possibility of intravascular conversion of fibrinogen to fibrin (Schneider 1959) There is also reason to consider whether administration of *antifibrinolytics*, such as epsilon aminocaproic acid, is indicated before delivery, as such a treatment will counteract the fibrinolysis which is endeavouring to re-dissolve the formed fibrin

After the delivery the approach is entirely different Now, there is no longer a risk of massive entry of thromboplastin into the blood stream Therefore fibrinogen therapy appears to be indicated and not to involve any notable risk, at least not from a coagulation point of view If fibrinolysis is still active at this time, it should be counteracted by the administration of epsilon aminocaproic acid since otherwise it may cause a continued bleeding tendency (Albrechtsen and Skjødt, 1962)

The investigations of the vaginal blood in the present case gave results in accordance with previous studies (Albrechtsen and Skjødt, 1962) and indicate that a coagulation process had taken place in the uterus presumably caused by release of thromboplastin from the placenta In accordance with previous studies no fibrinolytic activity was found in the vaginal blood

SUMMARY

A case of abruptio placentæ with hæmorrhagic diathesis and hypofibrinogenæmia is reported

Investigations of the coagulation components of the blood and a

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SUMMARY

A case of abruptio placentæ with hæmorrhagic diathesis and hypofibrinogenæmia is reported

Investigations of the coagulation components of the blood and a

number of severe complications during administration of human fibrinogen before delivery indicate that in this case the hæmorrhagic diathesis was caused by intravascular coagulation with secondary fibrinolysis

Accordingly, it must be carefully considered whether infusion of fibrinogen before delivery is justified in severe cases of abruptio placentæ On the other hand, treatment with fibrinogen may be indicated after delivery, when the risk of intravascular conversion of the administered fibrinogen to fibrin is very slight

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From The Department of Obstetrics and Gynæcology The General Hospital Malmo (The Late Professor Sune Genell and Professor Stig Kullander)

OBSTETRIC STUDIES IN WOMEN WITH RENAL DISEASE IN CHILDHOOD

BY

CARL FELDING

The problem which will be dealt with here forms part of a more extensive work entitled "Obstetric studies in women with histories of renal disease" An account will be given of the course of the delivery and complications in women who had sustained some form of renal disease prior to the age of 15 years

The Material consists of 120 women with 192 deliveries who had previously had renal diseases diagnosed and treated in hospital The material was obtained by review and follow up of all the case histories from The Children s Hospital in Malmo between 1932 and 1942 of girls with some form of renal disease and from these patients who had born children were selected The maternity case histories were then studied in relation to various complications, particularly the maternal and infantile mortalities prematurity and eclampsia Further by review of all the case histories from the Department of Obstetrics in Malmo during the period 1950—1961 patients who stated on admission that they had had renal disease in childhood were recorded In cases in which further information in the form of a hospital case history was available this was obtained In the present work only cases treated in hospital both for the renal disease and the delivery are included

Patients who did not give birth are thus *excluded* Thus a form of selection has taken place It appears reasonable to presume that many patients with serious renal disease became sterile or

did not desire pregnancy, had applied for legal termination of pregnancy or had spontaneous miscarriages Many may have died from the original disease It is thus impossible to draw any conclusions concerning the long-term prognosis of renal disease in children from this material and this task is thus outside the scope of the present investigation

Women with urinary infections in childhood

In pædiatric literature concerning the long-term prognosis of pyelonephritis in girls, the problem of future pregnancies is not dealt with systematically This is probably due partly to the fact that pregnancy in the adult woman is not primarily a pædiatric problem and partly because attention was first drawn to chronic pyeolonephritis as a disease entity *in recent decades*

Wharton *et al* (1937) accounted for the long-term prognosis in 30 girls with pyelonephritis Of these, however, only three had become pregnant by the time of follow-up examination One had sustained recurrence of the urinary infection during pregnancy Woodruff (1954) had access to more than 76 cases and in cases with recurrent urinary infections he demonstrated a considerable increase in the incidence of urinary infection in connection with pregnancy and delivery and demonstrated renal changes at follow-up examination He also found no such complications in patients with histories of only one attack of infection

Rauramo *et al* (1962) collected a series of 541 patients who had sustained nephritis or pyelonephritis and assessed the fertility, incidence of toxæmia, mortality and the prognosis for the infant These authors demonstrated that the prognosis as regards the delivery both for mother and child is better if a considerable period (more than three years) has elapsed between the renal disease and the pregnancy Their material includes however only nine patients who had pyelonephritis prior to the age of 15 years and who became pregnant later in life These nine patients were delivered of ten infants with no maternal mortality

In the present series, the incidence and frequency of urinary infection in pregnancy in such women unfortunately cannot be

illustrated This is because many patients attended for antenatal control examinations outside hospital

In urinary infections in the puerperium, the urinary sediment was only investigated in cases of proteinuria, pyrexia or subjective urinary symptoms In this manner many symptomless cases of bacteriuria have probably passed undiagnosed through the maternity departments and the urinary findings thus accounted for are of limited value

Further no reliable figures for the incidence of abortion are available

Seventy-one patients with some form of urinary infection all of whom were under the age of 15 years at the commencement of the illness are included in the series Children under the age of three years were only very rarely submitted to urography or extensive investigations in addition to the usual urinary investigations The 71 patients included in the series had the following common symptoms *pyuria* determined on the voided urine and, in addition bacteriuria usually determined on examination of sediment in a catheter specimen and also by culture Quantitative determination of the bacterial count was not undertaken

The symptomatology was very variable Where there was a definite history of pyrexia or where the temperature chart showed this the case was registered here as "acute pyelonephritis" A total of 47 such cases were recorded Afebrile cases are termed here "apyrexial urinary infections" and comprise 14 cases In addition the material includes a third minor group with a protracted course recurrent acute attacks during several years or prolonged and occasionally therapy resistant urinary infections persisting over a series of years These patients have probably chronic pyelonephritis and will be termed here "protracted urinary infection There were ten such cases

Half of the patients were under the age of three years when the disease was diagnosed This age-limit is of practical significance in that the older the child the more completed was the investigation

Twenty five patients were submitted to urography In nine cases pathological findings were revealed post nephrectomy status in four hydronephrosis in four papillary necrosis in one

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Maternal Childhood Diagnosis	No Women	No Alive	Infants Dead	Birth Weight >2 500	Birth Weight <2 500	Total No Infants
Acute Pyelonephritis	47	73	3	73	3	76
Apyrexial Urinary Infections	14	24	0	21	3	24
Protracted Urinary Infections	10	16	1	16	1	17
Total	71	113	4	110	7	117

The perinatal mortality was thus four out of 117 infants=3 6 per cent

The incidence of premature infants (birth weight under 2,500 g) was seven out of 117=6 per cent

For rough comparison it may be mentioned that the perinatal mortality in The Department of Obstetrics in Malmo in 1938—1960 was 2 8 per cent and the incidence of prematurity was 5 9 per cent

In this connection it is of interest to elucidate the circumstances involved in the perinatal infantile deaths in order to illustrate if possible the extent to which the renal disease in the mother may have contributed to or caused the death One patient (S born 1935) had two dead infants The mother had had acute pyelonephritis at the age of three years with pyrexia Since then she had been symptom free Urography was not carried out In 1959 she had a premature delivery with seropositive syphilis The infant weighed 1 900 g was born two weeks before term and died after delivery Autopsy revealed cystic kidneys diaphragmatic hernia and pulmonary atelectasis but no evidence of syphilis During the subsequent pregnancy in 1960 the patient was submitted to operation for a right ovarian cyst (right salpingoophorectomy) Pregnancy continued but intrauterine fœtal death occurred five months later The fœtus weighed 2 450 g and was macerated but did not reveal either deformities or syphilis Patient H born 1933 had acute pyelonephritis at the age of seven months It was stated that she had been symptomfree since then In her first pregnancy in 1956 the infant died during delivery Autopsy revealed asphyxia with the umbilical cord four times round the neck but no deformities In 1959 and 1961 this patient had two entirely normal pregnancies resulting in living infants Patient B born 1937 is accounted for among the case

malrotation in one and local shrinkage suggestive of scarring after pyelonephritis in three patients

Prognosis for Delivery

The 71 women had a total of 116 deliveries with 117 children No obstetric deaths occurred among the mothers but one woman died from uræmia nine months after delivery The other relevant obstetric complications were as follows

Intrapartum eclampsia	1
Severe pre-eclamptic toxæmia	1
Slight pre-eclamptic toxæmia	3
Urinary infection during the puerperium	4

It is difficult to compare the incidence of the complications with the total clinical material as the classification during the period in question varied somewhat, e g the subdivision of cases of toxæmia In the present material, Dieckmann's classification from 1952 was employed The incidence of eclampsia in the Department of Obstetrics in Malmo during the period 1938–1960 was 139 per 69,586 deliveries, giving a ratio of 1 500

The details of the patient who died from uræmia are reported among the case histories (page 146) The patient who developed eclampsia had a urinary infection with pyrexia at the age of one year Her first confinement, in 1952 was complicated by eclampsia Urinary infection occurred during pregnancy and in the puerperium In 1955, a therapeutic abortion was undertaken In 1957, the patient had a normal delivery with slight proteinuria but no urinary infection and no hypertension Thus, in this case, the renal disease and the eclampsia did not prevent a normal delivery five years later

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The result of the deliveries as regards the perinatal mortality and prematurity appears from the following Table

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7 *L born 1938* In the Children s Hospital with the diagnoses of left sided pulmonary tuberculosis and acute pyelitis in 1940—1942 During this two year period in hospital there were several attacks of pyrexia and pyuria In 1949 pain in the back fatigue with high ESR and pyuria developed Urography revealed bilateral nodular renal pelves In 1960 normal delivery of a female infant weighing 3 350 g No toxaemia occurred but renal infection *was present* during the puerperium

8 *K born 1939* Since the age of 13 years this patient had experienced re current urinary symptoms with sudden pyrexia and lumbar pain In 1958 normal delivery of a female infant weighing 4 330 g with no associated proteinuria or pyrexia In 1959 right renal hydronephrosis with high origin of the ureter was diagnosed Following a plastic operation *on the renal pelvis* the *urine* became *sterile* but urography revealed deformity and cicatricial con traction of the upper calyx In 1960 and 1961 two deliveries without com plications In 1962 progressive changes in the right kidney were revealed radiologically as compared with the plates from 1959

9 *H born 1940* Since the age of three years proved urinary *infection* hydronephrosis and reduced renal function with raised *residual ni trogen* and serum creatinin Delivery *in 1961 of* female infant weighing 3 050 g During pregnancy hypertension of 105/105 which disappeared on conservative therapy before delivery Otherwise the course was normal Serum creatinin was maxi mally 1 83 and residual nitrogen 43 during the puerperium Continual proteinuria of 1—2 ‰

10 O *born 1941* At the age of two years acute *pyelonephritis During* childhood recurrent attacks Urography *in 1957 revealed* papillary necrosis Delivery in 1959 wi hout pre-eclampsia or urinary symptoms with birth of female infant weighing 4 000 g Urography in 1960 showed papillary necrosis

Discussion

The series consists of 71 women who had sustained urinary infections in childhood with 116 deliveries and 117 infants The investigation reveals that a urinary *infection* in childhood is scar cely of any significance for the result of delivery in the adult woman Of particular interest are reports of ten cases with previous prolonged urinary infections in whom 16 deliveries (17

histories (see below, no 6) In this patient also, a subsequent pregnancy was normal

The ten cases which were registered as "protracted urinary infections" are of the greatest obstetric interest and will be detailed below

1 O, *born 1907* "Pus in one kidney" in 1919 at the age of 12 years Treated in The Children s Hospital *Since then persistent proteinuria In hospital f r* the same condition in 1925 Pregnant in 1936 with delivery of a male infant weighing 2,940 g Continual proteinuria (2—4 ‰) prior to and after delivery no hypertension and no pre eclampsia but high pyrexia during puerperium (partly on account of mastitis and partly on account of urinary infection) Discharged "in poor condition" Death from uræmia six months later Autopsy revealed advanced bilateral pyelonephritis

2 W, *born 1919* Right sided nephrectomy at the age of 14 years because of pyelonephritis Three years later (1937) left nephrolithiasis and left pyelonephritis *Urography revealed double renal pelvis in the remaining kidney* Left ureterolithiasis in 1938 In 1941 therapeutic abortion because of renal disease In 1946, delivery of male infant weighing 3 300 g No pre eclampsia In 1947, normal delivery Blood pressure 120/85 no proteinuria

3 S, *born 1921* From the age of ten years numerous periods in hospital in surgical wards with the diagnoses of cystopyelitis left ureteric calculus and chronic pyelitis In 1945 operation for bilateral ureterocele and in 1949 right pyelolithotomy In 1950 scanty proteinuria continual pyuria and bacteriuria Urography bilateral hydronephrosis, deformity of right kidney and dilatation *of left ureter In 1953, normal delivery of male infant weighing 3 600 g No pre* eclampsia but persistent constant pyuria and bacteriuria In 1958 urography revealed irregular contours left kidney smaller than the right and the parenchyma very thin in patches No concretions No increase in blood pressure, serum creatinin or residual nitrogen demonstrated at any time

4 P *born 19 9* At the age of 11 years right nephrectomy was performed for chronic pyelonephritis At pre-operative urography the left kidney was considered to be normal but on subsequent examination of the photographs thin parenchyma suggestive of pyelonephritic scarring could be demonstrated *Nineteen years later (1959) the patient was delivered of a female infant* weighing 3 900 g No pre-eclampsia In 1961 another normal delivery with normal urinary findings and blood pressure

5 M *born 1933* At the age of two years the patient was in hospital with the diagnosis of right nephrolithiasis She then had an urinary infection with pyrexia At the age of five years "chronic cystopyelitis with exacerbations At that time scanty proteinuria and pyuria were found Straight X ray of kidney regions *revealed kidneys of normal size and configuration* In adult life, two deliveries which were normal in all respects During the intervening period, the patient was well and experienced no renal symptoms

6 B, *born 1937* At the age of five years recurrent acute attacks of pyelone

The patient with "severe" pre eclampsia (H born 1912) had had proteinuria since 1922 In 1934 she was in hospital with the diagnosis of "chronic nephritis with exacerbations" She had then a blood pressure of 145/100 and proteinuria In the urinary sediment numerous red and white cells and cylinders were found but no bacteria The maximum urinary pecific gravity was 1 023 In her first pregnancy in 1935 she had a normal blood pressure but increasing proteinuria (no urinary infection) of as much as 8 ‰ Five years later she had another pregnancy with increase of blood pressure to 170/115 and proteinuria of 8 ‰ still with no signs of urinary infection On both occasions the infants were healthy and of normal weight The "toxæmia" appears to have been an "aggravation" of the chronic nephropathy already present The remaining cases of pre eclampsia were milder and more transient in nature

The infantile prognosis appears from the following Table

No Al e	I f nts Dead	B rth > 2 500	Weigh s 2 00 g	Total No Infants
60	2	57	5	62

The perinatal mortality was thus two out of 62=3 2 per cent Incidence of premature infants (under 2 500 g) was five out of 62=8 per cent

The histories of the patients with the dead infants will be described briefly

1 B bo n 1940 At the age of e ght years acute glomerulonephr tis two weeks after an infect on of the upper resp ratory tract Adm tted w th hæma tur a and prote nur a of 2 5 ‰ ESR 65 mm In hospital for two months during wh ch the sediment became normal but the proteinur a pers sted In 1958 premature del very Fœtus we ghed 1 470 g and d ed postnatally No signs of pre-eclampsia during del very

2 L born 1941 Th s pat ent was in hosp tal for six months at the age of n ne years on a count of prote nuria and hæmaturia Two years later increa ed numbers of red blood cells in quant tat ve sed ment and slight proteinur a w th normal abil ty to concentrate In 195 and 1960 normal del ver es In 1962 premature del very w th fœtal we ght of 1 530 g The infant d ed post natally Autopsy re ealed atelectas s and hyal ne membrane

It is d fficult to express an opinion concerning the extent to which the maternal renal disease influenced these deliver es In the second case there is no apparent connection

infants) later occurred In these cases, one perinatal infantile death occurred but there were no cases of severe pre-eclampsia

It must be emphasized that the material does not permit any evaluation of the long-term prognosis of pyelonephritis in girls, simply because patients who have not had children are not included in the material The fate of these patients is unknown both as regards the further progress of the renal disease and its influence, if any, on the absence of reproduction

Women with glomerulonephritis in childhood During analysis of the case history material, 41 patients were encountered with glomerulonephritis who, in adult life, had at least one delivery

The diagnostic criteria were proteinuria and hæmaturia without demonstrable infection Most frequently, the disease occurred in connection with infection of the upper respiratory tract, tonsillitis or scarlatina In 12 patients, hypertension and/or increase of residual nitrogen occurred In 13 cases, definite signs of œdema were present In the majority of cases, the symptoms disappeared in the course of 1—5 months but, in 13 cases, proteinuria and hæmaturia persisted after six months and were occasionally permanent or at least uninterrupted until delivery In six cases, urographic investigation had been undertaken, the findings being normal in five cases while in one patient bilateral malrotation was present Twelve of the patients were examined for antistreptolysin titre and 11 were found to be positive

On review of the case histories, a number of obscure cases were excluded which may have been cases of glomerulonephritis but in which the criteria mentioned above were not fulfilled

Prognosis regarding delivery

These 41 patients who had had glomerulonephritis prior to the age of 15 years had 62 deliveries with 62 infants There were no maternal deaths and no cases of eclampsia but, on the other hand, the following complications occurred

Severe pre-eclamptic toxæmia	2 (the same patient in two deliveries)
Slight pre-eclamptic toxæmia	6
Urinary infections in the puerperium	6

The patient with "severe" pre-eclampsia (H, born 1912) had had proteinuria since 1922 In 1934 she was in hospital with the diagnosis of "chronic nephritis with exacerbations" She had then a blood pressure of 145/100 and proteinuria In the urinary sediment, numerous red and white cells and cylinders were found but no bacteria The maximum urinary specific gravity was 1 023 In her first pregnancy in 1935 she had a normal blood pressure but increasing proteinuria (no urinary infection) of as much as 8 ‰ Five years later she had another pregnancy with increase of blood pressure to 170/115 and proteinuria of 8 ‰ still with no signs of urinary infection On both occasions the infants were healthy and of normal weight The "toxæmia appears to have been an "aggravation" of the chronic nephropathy already present The remaining cases of pre eclampsia were milder and more transient in nature

The infantile prognosis appears from the following Table

No Alive	Infants Dead	Birth >2 500	Weights <2 500 g	Total No Infants
60	2	57	5	62

The perinatal mortality was thus two out of 62=3 2 per cent Incidence of premature infants (under 2,500 g) was five out of 62=8 per cent

The histories of the patients with the dead infants will be described briefly

1 *B born 1940* At the age of eight years acute glomerulonephritis two weeks after an infection of the upper respiratory tract Admitted with hæmaturia and proteinuria of 2 5 ‰ ESR 65 mm In hospital for two months during which the sediment became normal but the proteinuria persisted In 1958 premature delivery Fœtus weighed 1 470 g and died *postnatally* No signs of pre eclampsia during delivery

2 *L born 1941* This patient was in hospital for *six months* at the age of nine years on account of proteinuria and hæmaturia Two years later increased numbers of red blood cells in quantitative sediment and slight proteinuria with normal ability to concentrate In 1957 and 1960 normal deliveries In 1962 premature delivery with fœtal weight of 1 530 g The infant died post natally Autopsy revealed atelectasis and hyaline membrane

It is difficult to express an opinion concerning the extent to which the maternal renal disease influenced these deliveries In the second case there is no apparent connection

Discussion

Forty-one patients who had had glomerulonephritis in childhood were delivered of a total of 62 infants in adult life without any maternal mortality and with no cases of eclampsia The perinatal mortality was 3 2 per cent and the incidence of infants with birth weights of less than 2,500 g was 8 per cent As in the case of pyelonephritis, no similar series appear to have been described in the literature Rauramo (1962) accounted for 28 patients who had sustained glomerulonephritis prior to the age of 15 years and who later were delivered The results in these particular cases are not specified in the tables but are recorded together with the cases of nephritis in adult women In other publications on the same subject, the age group is not described precisely (Kaplan, 1962, and Rudebeck, 1946) and in investigations concerning the long-term prognosis for girls with glomerulonephritis, the obstetric consequences are seldom considered In the material presented here, no evidence is found suggesting that glomerulonephritis in childhood seriously influences a subsequent delivery

Orthostatic albuminuria in childhood

Systematic review of the case histories of all the girls who had been in hospital for renal disease or suspected renal disease revealed a number of cases in which renal investigation demonstrated proteinuria in the upright position but not in the prone position, characterized as "orthostatic albuminuria" In the primary review of the case history material, such cases were deliberately included in order to ensure that there were no patients in this group who actually had renal disease or who developed renal disease later in life

Eight cases were followed up to one or more deliveries which occurred, on an average nine years after the patients had been in hospital because of orthostatic albuminuria At the time of preparation of this paper, these eight patients had had a total of 14 deliveries No cases of prematurity nor maternal nor infantile deaths were encountered and all of the infants weighed over

2,500 g No cases of toxæmia of pregnancy occurred None of the patients had, as far as is known, any renal disease during the intervening period

SUMMARY

A series of 120 patients who had been admitted to hospital prior to the age of 15 years in 1933—1942 (71 patients classified as urinary infections, 41 classified as glomerulonephritis and eight as orthostatic albuminuria) were followed up until adult (fertile) life and their deliveries (192 in all) were studied in relation to toxæmia prematurity maternal and infantile mortalities No maternal deaths occurred but one case of eclampsia was recorded The perinatal mortality and the prematurity rate are detailed

No definite deterioration of the obstetric prognosis (as compared with a total series) could be demonstrated in these women who had sustained renal disease in childhood

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OBSTETRIC STUDIES IN WOMEN AFTER NEPHRECTOMY

BY

CARL FELDING

The material presented here is part of a more extensive work entitled 'Obstetric studies in women with histories of renal disease" The present series comprises 36 women, all of whom had been delivered of at least one infant after nephrectomy had been performed The object of the investigation was to assess whether the incidence of toxæmia of pregnancy, the maternal and infant mortalities or the incidence of prematurity was increased in such cases

The first record of delivery after nephrectomy was described by Shepherd (1890) Hartmann (1912) later dealt with the problem in two articles and collected the literature from 1893-1912 Hartmann concluded that the obstetric prognosis is good and that there was no demonstrable difference in the pregnancies and deliveries in women with either right or left-sided nephrectomies Pousson (1913) considered that the risk of infection was greater in the right than the left kidney and that the obstetric prognosis was, therefore, better in patients in whom right sided nephrectomy had been undertaken Dippel (1951) also found increased risk of infection in the remaining right kidney and Nobili and Finotti (1955) share this opinion In an obstetric material Schaefer *et al*, (1954) found an incidence of pregnancy after nephrectomy of 1 3,080 which was, however, only in women in whom nephrectomy had been undertaken on account of renal tuberculosis Israel (1911) emphasized the necessity of culture of the urine for tubercle bacilli after nephrectomy because of the risk of renal tuberculosis but considered the obstetric prognosis to

be otherwise good Other authors from the same period are of the same opinion (Matthews 1921, Borelius, 1924)

Matthews (1921) considered that pregnancy may be permitted three years after the nephrectomy and that therapeutic abortion is indicated if the function of the remaining kidney is inadequate Fabignon (1933) reports the case histories of 21 women in whom nephrectomy had been undertaken who were delivered of 18 living infants Smith (1949), Welsh, Wellen and Taylor (1944) del Valle y Adara (1950), and Schrewe (1950) dealt with the problem of delivery after nephrectomy as part of wider investigations into the course of pregnancy in women with renal disease Macquet (1956) described 14 cases in which nephrectomy had been undertaken on account of renal tuberculosis In two of these cases toxæmia developed during subsequent pregnancy

According to Kittredge and Crawley (1956), 18 months should elapse between nephrectomy and a subsequent pregnancy in order to permit the remaining kidney to hypertrophy Batalla Sabate (1951) considers one year to be a suitable period in most cases but three years in the case of renal tuberculosis

Material

During the period 1932–1956 60 women under the age of 40 years were submitted to nephrectomy in The Department of Surgery in Malmo Twenty nine of these patients subsequently had at least one delivery Further review of 37 662 deliveries in The Department of Obstetrics and Gynæcology in Malmo from the years 1950–1961 revealed 19 women in whom nephrectomy had been undertaken Many of these were however, also included in the first group of 29 cases mentioned above Several cases were put at the disposal of the author from The Department of Obstetrics and Gynæcology in Lund Altogether hospital cases histories were available concerning both the renal disease and the deliveries for 36 patients

The incidence of nephrectomy among parturient patients in Malmo was 19 out of 37,662, corresponding to 0 5 ‰ Nobili and Finotti (1955) found an incidence of 0 95 ‰ in a series of 25 237 cases

Obstetrical Data In Table I an account is given of the result of the first delivery after nephrectomy This of course does not signify the first pregnancy in all of the cases The Table shows that the average age of the patients was 23 8 years at nephrectomy with a range from 12–35 years and that the age at the first subsequent delivery was 30,5 years (range 20–39 years)and that the interval between nephrectomy and delivery was 6–7 years (range 2–18 years)

Twenty-eight patients were nulliparous at the time of nephrectomy The remainder, *i e* eight patients had had 1–2 deliveries prior to nephrectomy Rightsided nephrectomy had been undertaken in 19 and leftsided nephrectomy in 17 patients The indications for operation were renal tuberculosis in eight, pyonephrosis in eight, hydronephrosis in nine, nephrolithiasis in four, pyelonephritis in six cases and renal cancer in one In the 36 deliveries, 37 infants with an average birth weight of 3,350 g were delivered The uncorrected perinatal mortality was three out of 37 (8 1 per cent) In two cases, severe pre eclamptic toxæmia (Dieckmann, 1952) developed and in eight cases instrumental delivery was required

16 patients had more than one delivery after nephrectomy The total number of infants born thus becomes 55 In order to assess the success of the delivery, as judged by the condition and weight of the infant at birth, three cases in which the pregnancy ended with death of the infant are examined in more detail

A, born 1916 (no 10 in Table I) Submitted to operation in 1944 for right hydronephrosis Delivery in 1953 nine years after operation At delivery proteinuria of 3 2 ‰ and blood pressure 170/110 were recorded A macerated male infant was delivered birth weight 2 380 g No urinary infection Two years later, normal delivery of female infant weighing 3 210 g In this latter puerperium urinary infection and leftsided pyelonephritis occurred

B born 1916 (no 11 in Table I) Nephrectomy in 1950 for right hydronephrosis Forceps delivery in 1955 Fœtus died during delivery and autopsy revealed aspiration Neither pre-eclamptic toxæmia nor urinary infection occurred Three years later spontaneous delivery of living male infant weighing 3 420 g

C, born 1930 (no 32 in Table I) Nephrectomy in 1948 for leftsided pyelonephritis Deliveries in 1953 and 1955 Both infants died from erythroblastosis due to maternal Rh immunization In 1958 however the patient was delivered of a living Rh negative female infant weighing 3 750 g

The total perinatal mortality was four out of 55 infants (7 3 per cent) but, if correction for the cases of erythroblastosis is made, the mortality becomes two out of 53 infants (3 4 per cent)

Seven of the patients in the material had undergone an abortion, either legal or spontaneous, after the nephrectomy (nos 5, 15, 20, 23 26, 28 and 34)

The 36 women in the series are, of course, the result of certain selection The patients involved were not greatly influenced by the original condition and they desired to become pregnant

Urological Date The diagnosis of renal disease is frequently difficult and, not uncommonly is presumptive In this series, however, more than the routine investigations were undertaken The most important methods of investigation in this connection thus consisted of urography, pathological examination of the extirpated kidney and culture of the urine

In 32 out of the cases pre-operative urography was undertaken and normal morphology was found in the healthy kidney in 27 In five cases, however changes were present construction at the junction between the renal pelvis and the ureter (nos 14 and 17 in Table I) malrotation (no 34) double renal pelvis (no 17) and stone formation (no 15)

In 26 out of the 36 cases, pathological reports on the operation specimen are available On the other hand, no data are available concerning the remaining kidney during the time prior to and during the subsequent pregnancy Reliable information concerning the incidence of pyelonephritis stone formation or renal complications during pregnancy is not available in this material

If instead of assessing the significance of the nephrectomy for the subsequent pregnancies, an attempt is made to assess the influence of pregnancy upon the remaining kidney the problem becomes quite different No reliable information on this subject is available in the present material In four of the patients, however, certain data are available concerning the urological status of the patients after delivery

A born 1922 (no 21 in Table I) Nephrectomy in 1955 on account of coralline calculus Normal delivery in 1958 Control examination in December 1958 No albumin, sediment normal Urography normal remaining left kidney

B born 1928 (no 28 in Table I) Nephrectomy in 1950 on account of

Table 1 36 Women Who Had Undergone Nephrectomy before Conception Result of the First Delivery after Nephrectomy

	Year of Birth (Mother)	Age at Nephrectomy	Parity at Nephrectomy	Indication	Site	Age at Delivery	Interval Nephr./Delivery	Weight of Infant	Obstetric Complications	Maximum BP
1	03	27	0+0+0	Nephrolithiasis	R	35	8	3610	0	?
2	03	27	1+1+0	Pyonephrosis	L	33	6	3200	0	145/90
3	05	35	1+0+0	Tuberculosis	R	39	4	3540	Hæmorrhage 600 ml	160/110
4	11	22	0+0+0	Tuberculosis	L	29	7	4460	Threatened asphyxia of fœtus	135/90
5	12	28	2+0+0	Tuberculosis	L	35	7	3070	0	130/80
6	13	24	2+0+0	Pyonephrosis	R	35	11	3730	0	115/75
7	13	24	0+0+0	Tuberculosis	R	32	8	4100	0	130/90
8	14	24	0+0+0	Pyonephrosis	L	37	13	3750	Retained placenta Proteinuria 1‰	Normal*
9	15	28	0+0+0	Pyonephrosis	R	31	3	3610	Threatened perineal rupture	145/110
10	16	29	0+0+0	Hydronephrosis	R	37	9	2380 Died	Toxæmia Fœtus macerated	170/110
11	16	34	0+0+0	Hydronephrosis	R	39	5	3450 Died	Aspiration Forceps	130/90
12	16	27	1+1+0	Pyonephrosis	I	35	7	1820+2060	Twins	145/110
13	16	25	0+0+0	Pyelonephritis	R	27	2	3285	0	140/90
14	17	35	0+0+0	Hydronephrosis	I	37	2	2870	0	140/80
15	19	14	0+0+0	Pyelonephritis	R	27	13	3300	Threatened asphyxia of fœtus Forceps	?
16	19	16	0+0+0	Tuberculosis	I	25	9	3630	Weak pains Forceps	?
7	20	34	0+0+0	Pyelonephritis	R	36	2	3400	0	150/100
	20	12	0+0 0	Hydronephrosis	R	28	16	4140	0	135/90
	21	27	0+0+0	Nephrolithiasis	I	36	9	2900	0	120/80
[illegible]	22	22	0+0+0	Nephrolithiasis	R	33	11	3060	Proteinuria 3‰	140/80
21	22	33	1+0+0	Nephrolithiasis	R	36	3	3020	0	130/80
22	23	23	0+0+0	Pyonephrosis	I	25	2	3100	Threatened fœtal asphyxia Forceps	130/[illegible]
3	25	24	0+0+0	Tuberculosis	R	39	6	28[illegible]	0	1[illegible]/—
[illegible]	[illegible]						[illegible]	[illegible]	The[illegible]	[illegible]

25	26	26	o+o+o	Hydronephrosis	R	29	3	3850	Weak pains Forceps Prote nuria o 3 oo	115/65
26	26	18	o+o+o	Tuberculosis	R	20	2	3850	o	1 0/80
27	27	25	1+o+o	Pyonephrosis	L	27	2	2800	o	130/75
28	8	22	o+o+o	Hydronephrosis (Pelvic Kidney)	L	8	6	3560	Threatened fœtal asphyxia Forceps	125/80
9	9	19	o+o+o	Pyelonephritis	R	32	13	3750	Weak pains Vacuum extraction	140/100
30	29	19	o+o+o	*Tuberculosis*	L	32	13	3620	o	165/85
31	29	12	o+o+o	Pyelonephritis	R	30	18	3900	Weak pains Vacuum extraction	130/80
32	30	18	o+o+o	Pyelonephritis	L	23	5	4310 *Died*	Rh immunization	140/95
33	31	27	o+o+o	Malignant Nephroma	L	30	3	3020	o	105/80
34	36	20	o+o+o	Pyonephrosis	R	25	5	34 0	o	130/80
35	38	20	o+o+o	Hydronephrosis	L	24	4	2770	o	120/80
36	40	17	o+o+o	*Hydronephrosis*	L	20	3	3330	Toxemia Proteinuria 1 o	165/120

o+o+o=No pregnancies

1+1+1=1 Delivery 1 Abortion and 1 Extra uterine pregnancy

Table 1 36 *Women Who Had Undergone Nephrectomy before Conception Result of the First Delivery after Nephrectomy*

	Year of Birth (Mother)	Age at Nephrectomy	Parity at Nephrectomy	Indication	Site	Age at Delivery	Interval Nephr / Delivery	Weight of Infant	Obstetric Complications	Maximum BP
1	03	27	0+0+0	Nephrolithiasis	R	35	8	3610	0	?
2	03	27	1+1+0	Pyonephrosis	L	33	6	3200	0	145/90
3	05	35	1+0+0	Tuberculosis	R	39	4	3540	Hæmorrhage 600 ml	160/110
4	11	22	0+0+0	Tuberculosis	L	29	7	4460	Threatened asphyxia of fœtus	135/90
5	12	28	2+0+0	Tuberculosis	L	35	7	3070	0	130/80
6	13	24	2+0+0	Pyonephrosis	R	35	11	3730	0	115/75
7	13	24	0+0+0	Tuberculosis	R	32	8	4100	0	130/90
8	14	24	0+0+0	Pyonephrosis	L	37	13	3750	Retained placenta Proteinuria 1 ‰	Normal
9	15	28	0+0+0	Pyonephrosis	R	31	3	3610	Threatened perineal rupture	145/110
10	16	28	0+0+0	Hydronephrosis	R	37	9	2380 *Died*	Toxæmia Fœtus *macerated*	170/110
11	16	34	0+0+0	Hydronephrosis	R	39	5	3450 *Died*	Aspiration Forceps	130/90
12	16	27	1+1+0	Pyonephrosis	L	35	7	1820+2060	Twins	145/110
13	16	25	0+0+0	Pyelonephritis	R	27	2	3285	0	140/90
14	17	35	0+0+0	Hydronephrosis	L	37	2	2870	0	140/80
15	19	14	0+0+0	Pyelonephritis	R	27	13	3300	Threatened asphyxia of fœtus Forceps	?
16	19	16	0+0+0	Tuberculosis	L	25	9	3630	Weak pains Forceps	?
	20	34	0+0+0	Pyelonephritis	R	36	2	3400	0	150/100
[illegible]	20	12	0+0+0	Hydronephrosis	R	28	16	4140	0	135/90
	21	27	0+0+0	Nephrolithiasis	L	36	9	2800	0	120/80
	22	22	0+0+0	Nephrolithiasis	R	33	11	3060	Proteinuria 3 ‰	140/80
21	22	33	1+0+0	Nephrolithiasis	R	36	3	3020	0	130/80
22	23	23	0+0+0	Pyonephrosis	L	25	2	3100	Threatened fœtal asphyxia Forceps	13[illegible]/[illegible]
3	25	24	0+0+0	Tuberculosis	R	3[illegible]	[illegible]	28[illegible]	0	130/—

mortality was 3 7 per cent None of the infants were born prematurely No relationship between the nature of the renal disease and prognosis of the delivery or difference between deliveries in women with right sided and left sided nephrectomies, respectively, could be demonstrated

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hydronephrosis and pelvic kidney Delivery in 1956 Control examination in 1960 normal findings on investigations for albuminuria, urine culture, blood pressure, ability to concentrate urine, serum creatinin and on urography

C, born 1930 (no 32 in Table I) Nephrectomy in 1948 for pyelonephritis. Deliveries in 1953 and 1955 with infant deaths on account of erythroblastosis Normal delivery in 1958 Control examination in 1956 serum creatinin urea clearence, ability to concentrate and urography were all normal

D, born 1936 (no 34 in Table I) *Nephrectomy in 1956 for pyonephrosis and horse shoe kidney Delivery in June 1961* Control examination in Novem ber 1961 *Serum creatinin 1 03* ability to concentrate and non protein residual nitrogen normal Urography showed good function

Discussion

The first description of nephrectomy with subsequent de livery was probably that by Shepherd in 1890 Since then, the problem has been dealt with partly as reports of cases and partly included in publications on subjects such as the long term prognosis of renal tuberculosis The general consensus of opinion seems to be that women in whom nephrectomy has been under taken negotiate pregnancy, delivery and the puerperium normally provided the function of the remaining kidney is not demonstrably affected In this connection the reservation must be made, however, that only rarely are the results of analysis of renal func tion immediately before and during pregnancy available The in cidence is approximately 0 5–1 ‰ in obstetric series *Different* opinions exist concerning the tendency to renal complications during pregnancy in women with right sided and left sided ne phrectomies, respectively

SUMMARY

The author has undertaken a prospective investigation of women in whom nephrectomy had been undertaken and who had conceived and undergone pregnancy and delivery after operation and also a retrospective review of 37662 obstetric cases From this material, it was found that all of the 36 women concerned were delivered of at least one living infant without any maternal mor tality and with no cases of eclampsia In two cases, however, severe pre-eclamptic toxæmia developed The corrected perinatal

mortality was 3 7 per cent None of the infants were born prematurely No relationship between the nature of the renal disease and prognosis of the delivery or difference between deliveries in women with right sided and left sided nephrectomies, respectively, could be demonstrated

Acknowledgement

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LAPAROSCOPY IN THE DIAGNOSIS OF ACUTE SALPINGITIS

BY

LENNART JACOBSON

"Even the most experienced gynecologists may be surprised to learn how much more accurate the visual sense is than that of their trained fingers"

R. W. TeLinde (1952)

The conventional approach to the diagnosis of acute salpingitis is based primarily upon three lines of enquiry—history, physical examination and laboratory investigations (Richardsson, 1957, Pinkerton, 1963, and others) This essentially clinical approach is often associated with difficulties and uncertainties In the absence of an objective diagnostic method it is obviously hazardous and of limited practical value to attempt to determine the relevance of various diagnostic criteria Furthermore, when it is recalled that acute salpingitis is increasing in frequency and that it has serious prognostic implications for the usually young women concerned, the need for a more accurate diagnostic method becomes apparent

Greater objectivity in diagnosis can be attained by exploration of the pelvic organs, a method not hitherto practised to any degree Routine exploratory laparotomy is clearly out of the question, but it is remarkable that very little use has been made of laparoscopic techniques Although some writers have drawn

attention to the possibilities offered by laparoscopy in this field (Hamilton, 1942, DeMiguel and Somoza 1959, Albano and Citadini, 1962, Espagno, 1962), the majority have regarded the method as inadvisable or contraindicated in the presence of acute inflammation of the pelvic or abdominal viscera (Guggisberg, 1956, Stamm, 1958, Frangenheim, 1959, 1960, 1962, Bennike, 1960, Morocz, 1962, and others) In the literature, however, no factual details are reported in support of this disapprobation

At the Department of Obstetrics and Gynæcology, Lund, laparoscopy, since its introduction in 1948, has been used in over 1 000 cases After the indications for its use had been successively extended, it became clear that examination in the presence of acute inflammation of the abdominal and pelvic viscera involved no added risk (Sjövall, 1954, 1959, 1960, Samuelsson, 1960) and in 1960 the method was adopted for routine use in the diagnosis of acute salpingitis From 1960 onwards, therefore, most of the cases seen in this department were diagnosed or confirmed visually

In this paper it is intended partly to present the satisfactory results obtained by this means and partly to evaluate the various conventional clinical diagnostic criteria in the light of the findings in a series of confirmed cases

Table I *Diagnostic Methods in 216 Cases of Acute Salpingitis seen in the Department of Obstetrics and Gynæcology Lund 1960–62*

	Acute Salpingitis		Total	Per cent
	gonococcal	non gonococcal		
Laparoscopy	81	104	185	97.2
Laparotomy	4	24	28	
Not explored	5	1	6	2 8

3 cases combined

Material

During the three year period 1960–62, a total of 216 patients suffering from acute salpingitis were treated in this department these form the basis for the present study As seen in Table I,

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sions or to evacuate an occasional tubo-ovarian abscess A clamp is routinely applied to the anterior lip of the cervix by means of which an assistant can manœuvre the uterus and improve the view for the operator A trained operator usually requires only 10–15 minutes to complete the procedure

Laparoscopic findings in acute salpingitis

Bennike (1960) claimed that laparoscopy is technically easy but that the visual findings are often difficult to interpret in terms of the various gynæcological disorders and that, therefore, much experience is required As regards acute salpingitis, however, it can be stated that the visual diagnosis is not normally difficult. Some doubts may be experienced when attempting to distinguish between very mild changes and normal cases All degrees of inflammation were seen in the present series but since laparoscopy was usually undertaken early in the course of the disease, the changes were most often of moderate degree The commonest findings were pronounced reddening and œdema of the tubes, giving them a distinctly swollen appearance These changes have come to be regarded as the minimum criteria for the diagnosis of acute salpingitis, since they have never been observed laparoscopically in definitely non inflammatory conditions In only two cases did these minimum criteria lead to a false negative diagnosis (see below) When tubal changes are very slight the possibility of a normal intrauterine pregnancy should be borne in mind since this can also give rise to increased vascular injection of the serosa albeit without œdema of the tubes In addition to the above, the following changes were also frequently seen in cases of acute salpingitis a sticky, sometimes fibrinous exudate on the surface of the tubes or between the tubes and the uterus fresh adhesions between the fimbriated ends of the tubes (or sometimes the tubes in their entirety) and surrounding structures pus in the pouch of Douglas or oozing out from the tubal ostia in more advanced cases, widespread adhesions, pyosalpinx or an inflammatory conglomeration of the entire adnexae In a few cases of gonorrhœal salpingitis the so-called violinstring" adhesions were seen between the peritoneum and the

the diagnosis was reached by means of laparoscopy in 182 cases, exploratory laparotomy was performed in 25 cases (on suspicion of acute appendicitis in most), and in three cases both these measures were undertaken In 6 cases the clinical picture was so *pronounced and fulminant that the diagnosis was* adjudged as beyond all doubt and no exploratory procedure was performed. Laparoscopy was thus performed in 87 3 per cent of cases and in 97 2 per cent some form of exploratory diagnostic method was used

Laparoscopic techniques

The routine employed in this department since 1960 is that cases with symptoms suggestive of acute salpingitis as well as cases *in which this disease* might be a differential diagnostic possibility with practically no exception are subjected to laparoscopy, usually on the day after admission, but occasionally on the third or fourth day, and before treatment is initiated The procedure is performed under general anæsthesia (although local anæsthesia is also suitable) and is preceded by bimanual examination of the pelvis after the patient is anæsthetized The skin incision is made in the mid-line immediately below the umbilicus If it is a repeat examination (laparoscopy was performed on two separate occasions in 17 cases because of acute salpingitis and on three occasions in one patient) the skin incision is made just above or just below the previous one In about 95 per cent of cases the technique and instruments used were as described by Ruddock (1937), whereas in the remainder a modified technique devised by Sjovall (1959) was employed In the latter, the laparoscope (a straight cystoscope or urethroscope can here be used instead) is inserted into the abdominal cavity by means of a loosely fitting trochar-tip which is used as a spear head and subsequently withdrawn by means of a previously attached thread Carbon dioxide is used for insufflation of the peritoneal cavity In about 70 per cent of cases a metal probe or stout canula was introduced about 10 cm to the right of the laparoscope, permitting the pelvic organs to be manipulated or specimens to be taken *for bacteriological examination* By this means it was also possible in some cases to part tenuous adhe-

FIGURES

surface of the liver as described by Curtis (1930) and Fitz Hugh (1934) More often in gonorrhoeal cases, however, similar, very long and tenuous adhesions were seen in the pelvis, together with moderate inflammation of the tubes Some typical laparoscopic pictures are shown in the colour plate

On the basis of the laparoscopic findings, the cases were classified into two groups, namely, 'salpingitis acuta levis" complying with the aforementioned minimal criteria only (23 per cent), and 'salpingitis acuta', *i e* the remainder, showing more pronounced inflammatory changes (77 per cent) These two groups did not differ vastly as regards the subsequent progress of the illness and it can be assumed, therefore, that we are here often concerned with different stages of the inflammatory process Thus, many cases classified as levis' would presumably have been found in the other group had laparoscopy been performed a day or two later Two cases with very slight inflammatory changes were classified as normal, but their subsequent course was such that the diagnosis of acute salpingitis reasonably could not be called in question This suggests that in these particular cases laparoscopy was performed too early, or that the operator was too stringent in his application of the diagnostic criteria

In most cases the view obtained through the laparoscope was excellent Laparoscopy was performed in 218 cases on the clinical suspicion of acute salpingitis (see further below) In 94 per cent of these the viewing conditions were entirely satisfactory, in 5 per cent they were less satisfactory due to adhesions or to technical difficulties and in 1 per cent no proper view was obtained because of multiple adhesions As a rule, the view obtained at laparoscopy is even better than that obtained at laparotomy, the former permitting a more detailed survey of the entire pelvic and abdominal cavity

Complications

In all, complications occurred in only 5 cases Three of these were insignificant (in 2 patients CO_2 was insufflated extraperitoneally into the abdominal wall and on one occasion trouble was experienced with the instrument itself) Only 2 patients

FIGURES

Fig 1 L A 20 yrs *Clinically suspected acute salpingitis* E S R 20 mm/hr Laparoscopic picture very slight reddening of the tubes but no œdema Classified as normal Patient left hospital 3 days later, free of symptoms Note the metal probe lifting up the proximal part of the left tube

Fig 2 M V, 25 yrs Non gonorrhœal acute salpingitis Palpable mass to the right of the uterus E S R 4 mm/hr Pronounced reddening and œdema of the right tube Turbid, bloody exudate in the pouch of Douglas

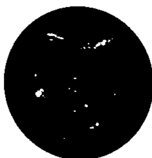
Fig 3 A P, 17 yrs Gonorrhœal acute salpingitis E S R 30 mm/hr The inflamed tube is seen surrounded by a sticky exudate

Fig 4 Same case as in Fig 2, showing typical sticky, thin adhesions between the left tube and surrounding structures

Fig 5 M N, 28 yrs Non gonorrhœal acute salpingitis E S R 5 mm/hr Moderate acute inflammatory changes of the tubes Fresh sticky, long and tenuous adhesions between the tubes and the uterus

Fig 6 B L, 15 yrs Gonorrhœal acute salpingitis No palpable mass E S R 15 mm/hr *Laparoscopically pronounced acute inflammatory changes* of the adnexæ On the right side, shown in the fig, the entire adnexa formed an inflammatory conglomeration with a thick fibrinous exudate on the surface





4





5





6

suffered physical discomfort In one of these a hæmatoma developed in the rectus sheath following accidental perforation of the inferior epigastric artery with the laterally inserted metal probe The hæmatoma was drained immediately and the patient made a rapid recovery In the other case, arterial hæmorrhage occurred from the cervix at the site of application of the volsellum This occurred while the patient was still in hospital, a week after operation Despite early ligature, the loss of blood amounted to nearly 1,000 ml but after transfusion, this patient also recovered rapidly On no occasion has damage been caused to intra abdominal organs and the symptoms of acute salpingitis have never been aggravated

Contraindications

In the literature, diaphragmatic hernia, marked circulatory failure and previous laparotomy or peritonitis have been quoted as contraindications to laparoscopy (*cf* Palmer, 1958, Bennike, 1960 Morocz, 1962) It may be said, however, that previous laparotomy is in our experience, a relative contraindication—each case must be assessed individually As a rule, laparoscopy should not be performed on patients who have previously been operated upon through a lower abdominal midline incision Previous laparoscopy, on the other hand, is not in our view a contraindication

Preliminary clinical diagnosis in laparoscopically proven cases of acute salpingitis

The indications for laparoscopy in the 185 cases of acute salpingitis diagnosed in this way (*cf* Table I) give a good idea of the accuracy of clinical methods of diagnosis in this disease In Table II these provisional diagnoses are listed and compared with the final laparoscopic diagnoses, the latter being classified as "acute salpingitis" normal findings and other disease respectively Laparoscopy was performed for "suspected acute salpingitis" in 218 instances Of these 71 per cent proved to be acute salpingitis while in 19 per cent no pathological changes were

Table II *Summary of All Cases Examined Laparoscopically in the Department 1960–62, and Their Relation to the Series of Acute Salpingitis*

Indications for Laparoscopy	Total Cases	Results				
		Acute Salpingitis	%	Normal	%	Other Diagnosis
Acute salpingitis?	218	155	71 1	42	19 3	21
Complications of acute salpingitis?	8	7	88	1	12	—
Acute salp ?/acute appendicitis?	19	8	42	2	10 5	9
Ectopic pregnancy?	106	6	5 7	52	49 1	48
Torsion of ovarian cyst?	6	3	50	1	17	2
Ovarian or adnexal tumour?	90	4	4 4	14	15 6	72
Endometriosis?	54	1	1 9	23	42 6	30
M H C-Granulosa cell tumour?	6	1	17	4	67	1
	507	185		139		183
(Other	229)					

found In the remainder, other conditions, several of a serious nature, were diagnosed There were, for instance, 6 cases of ectopic pregnancy (2 8 per cent), 2 cases of severe intra abdominal bleeding from ruptured corpus luteum cysts (0 9 per cent), 3 cases of ovarian abscess (1 4 per cent), 1 case of acute appendicitis and 1 case of endometriosis The laparoscopic examination had to be followed by laparotomy in 19 cases, mostly as a result of pathological conditions other than salpingitis, although in a few cases the reason was that profuse adhesions had prevented a diagnosis being reached laparoscopically It is of great interest and importance to note that normal pelvic conditions were found in no less than 42 cases (19 3 per cent) The rapid clarification of the diagnosis in many clinically misinterpreted cases thus made possible, conserves time, effort and hospital resources and is therefore in the best interests of both the patient and the hospital The question arises, however, as to what causes the clinical symptoms in those laparoscopically normal cases In about 25 per cent of cases a gonorrhœal infection of the vagina and cervix was found and might be incriminated, but in the remainder no definite cause could be found It should be mentioned in this context that of the 56 patients with acute

Table III *Laparoscopic Examinations and Presenting Symptoms in 56 Cases Admitted with Acute Gonorrhœa 1960–62*

Total number of cases	56
Number examined laparoscopically	10
Symptoms	
Acute abdomen*	17
Fever	12
E S R ≧ 15 mm./hr	18
Menstrual disorder	7

gonorrhœa admitted to the department during the period 1960–62 17 (30 per cent) had symptoms and signs of an acute abdomen on admission (Table III) As seen from the table, fever and a raised E S R were also common In 10 cases the initial symptoms persisted so long that laparoscopy was eventually undertaken, only to reveal that the pelvic organs were normal The subsequent clinical course invariably confirmed the negative findings It must be stressed, therefore, that the symptom-complex consisting of acute abdominal pain fever, raised E S R and Neisseria positive cultures from the vagina and cervix should not be unreservedly accepted as indicative of acute salpingitis

On 8 occasions laparoscopy was undertaken because of a clinical diagnosis of complications of acute salpingitis (Table II) Cases were allocated to this group when, in addition to acute salpingitis such conditions as oophoritis, ovarian or pelvic abscess etc were suspected Two such patients were indeed found to be suffering from large inflammatory swellings of the adnexæ, three had acute salpingitis of moderate severity, two had mild salpingitis and in one nothing abnormal was found This group also illustrates the difficulties attending the diagnosis of this disease by clinical means alone

Sometimes the diagnostic decision lies between acute salpingitis and acute appendicitis In such a situation laparotomy is commonly undertaken Laparoscopy, however offers a superior alternative As shown in Table II, 8 ca es of acute salpingitis were diagnosed and 2 cases could be pronounced normal by laparoscopic means in this group laparotomy was thus made unnecessary on 10 occasions (*cf* Hamilton 1942) It should be stressed in this connection that the appendix must be scrutinized

during laparoscopy when acute salpingitis is diagnosed, since the latter may be secondary to appendicitis and vice versa

As is also apparent from Table II, the diagnosis of acute salpingitis was reached unexpectedly in 15 cases during the course of laparoscopy performed for other reasons The aforementioned difficulties involved in diagnosing ectopic pregnancy became particularly apparent here

Those cases of laparoscopically diagnosed acute salpingitis constituted a relatively large proportion of all cases submitted to laparoscopy in this department, namely 185 out of 736, or 25 per cent This frequency shows a tendency to increase The variable, but not insignificant numbers of cases which could be pronounced normal in the various groups may partly be bound up with the liberal indications for laparoscopy, but they also, no doubt, underscore the difficulties and uncertainties involved in the clinical diagnosis and differential diagnosis of acute salpingitis

Clinical findings in acute salpingitis

Our experience with the laparoscope has led us to regard the clinical features of acute salpingitis as difficult to interpret and often misleading An analysis of all cases of acute salpingitis seen in this department during the period 1960–62 will serve to illustrate this point It will be seen that this series, comprising 216 cases (Table I), meets exacting requirements as regards objectivity 88 cases (40 7 per cent) were classified as gonorrhœal salpingitis after culture of gonococci from the vagina and/or cervix, the remaining 128 cases (59 3 per cent) were regarded as non-gonorrhœal As is well known, this distinction is doubtful at times and the question will be discussed again later Most of the patients were young, unmarried women Thus, 75 9 per cent were under 25 years of age Girls aged 15–19 years constituted no less than 45 4 per cent 77 3 per cent of the total were unmarried The cases labelled as gonorrhœal salpingitis were, on the average, younger and more often unmarried than were those classified as non gonorrhœal, the difference was statistically significant ($p < 0\ 001$)

Table IV Presenting Symptoms in the Whole Series of Acute Salpingitis

Presenting Symptoms	Acute Salpingitis gonococcal n = 88	Acute Salpingitis non gonococcal n = 128	Total Cases	Per cent
A) Acute abdomen	77	104	181	83 8
B) Other	11	24	35	16 2
atypical abdominal pain	6	11	17	7 8
menstrual disorder	5	8	13	6 0
malaise only	1	3	4	1 9
adnexal tumour unpainful	1	1	2	0 9
peritonitis		2	2	
urinary symptoms	1	1	2	
Bartholinitis		1	1	
prolonged diarrhoea	1		1	
resistant case from other hospital		1	1	
septic abortion	1		1	

The early clinical picture on admission is apparent from Table IV It was noted that only 84 per cent presented the classical feature of acute lower abdominal pain nausea and vomiting whereas Holtz (1930) and Hedberg and Spetz (1958) quoted a figure of about 95 per cent[1] This discrepancy may be the result of differences in diagnostic criteria In 16 per cent the illness appeared in another way thus, in 8 per cent the abdominal pain was diffuse in type and onset or was atypically localized, in 6 per cent the occurrence of irregular bleeding directed suspicion towards the possibility of ectopic pregnancy, in 2 per cent the only symptom was general malaise a few cases presented symptoms referable to the urinary or intestinal tracts, or other complaints tending to mask the real state of affairs

The onset of the disease was closely related to a menstrual period in 49 5 per cent of the patients This is lower than the corresponding figure in other published series—Hedberg and Spetz (1958) for example quoted a figure of 68 per cent Correlation with certain traditionally cited predisposing condi

[1] Concerning the clinical features of acute salpingitis the reader is also referred to a recent study by Viberg (Acta obst. et gynec scandinav 43 Suppl 4 1964) appearing after this paper had been submitted for publication

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peritonitis		2	2	
urinary symptoms	1	1	2	
Bartholinitis		1	1	
prolonged diarrhoea	1		1	
resistant case from other hospital		1	1	
septic abortion	1		1	

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gitis could probably have been reached by conventional, clinical means This figure must not be accepted without reservation, of course, but it probably gives a fairly accurate impression of the true situation Furthermore, even in these cases visual con firmation is a valuable means of securing the diagnosis

Bacteriological examinations of material from the vagina and cervix have proved of limited value in the diagnosis of acute salpingitis, and in elucidating the ætiologi (*cf* Ringrose, 1960, Riggs, 1962, and others) In cases of—by definition—gonorrhœal salpingitis, gonococci alone could be cultured from the cervix in 61 cases (69 per cent), while in the remainder a mixed growth of gonococci, coliforms and enterococci, staphylo and strepto cocci was obtained (Table VI) In only 58 of 128 cases (45 per cent) of so called non gonorrhœal salpingitis could pathogenic bacteria be cultured from the vagina and cervix The distinction between gonorrhœal and non gonorrhœal types of salpingitis is doubtful for several reasons A negative culture does not of necessity exclude a gonorrhœal infection (*cf* Miller, 1944, Riggs, 1962) On the other hand, the ætiological role of the gonococcus has not yet been satisfactorily explained although some suggest that it is to assist and pave the way for other types

Table VI *Bacteriological Findings in Acute Salpingitis Material Taken for Culture from Vagina/Cerıix and via Laparoscope from Pelıic Cavity respectively*

	Acute Salpingitis		Total Cases
	gonococcal	non gonococcal	
A) Cultures from vagina/cervix (all cases)			
gonococci only	61	—	61
coliforms enterococci	18	43	61
staphylococci and/or streptococci	10	26	36
no growth	—	70	70
B) Cultures from the pelvic cavity (39 cases)			
staphylococci and/or streptococci	2	2	4
coliforms enterococci	1	2	3
clostridium welchii		1	1
gonococci	1		1
no growth			
	14	15	29

tions was relatively low 5 1 per cent of cases developed after curettage, 1 4 per cent after *abortion*, 0 9 *per cent post partum* and 0 4 per cent after hystero salpingography Focal sepsis and generalized infections which could possibly have had causal significance were rare (3 cases) It was noteworthy, however, that many of the cases were in a poor state of dental hygiene Very often, however, acute salpingitis *nowadays should be regarded* as a venereal disease, even though the bacteriological mechanism *has not been fully* elucidated

In Table V certain more objective signs are summarized The most constant of these was a raised E S R (≶ 15 mm/hr) About 60 per cent of cases were febrile In about 50 per cent, tenderness of varying degree was elicited either unilaterally or *bilaterally on bimanual examination of the pelvic organs, although no mass or swelling could be detected* A palpable mass or swelling was relatively more common in the gonorrhœal cases, a finding which was pointed out also by Hedberg and Spetz (1958) As seen from Table V, even tenderness was occasionally lacking This underlines the difficulty in diagnosing salpingitis by vaginal examination 5 6 per cent of cases had normal temperature *and E S R, a further 4 2 per cent had besides no* palpable swelling It was calculated from the case notes that in roughly 66 per cent of cases a correct diagnosis of acute salpin

Table V *Clinical Findings in All Cases of Acute Salpingitis*

Clinical Findings	Acute Salpingitis gonococcal n = 68	Acute Salpingitis non gonococcal n = 128	Total cases	Per cent
E S R ≶ 15 mm./hr	80	101	181	83 8
Fever	57	74	131	60 6
Bimanual examination				
tenderness, without mass	38	69	107	49 5
palpable mass	50	56	106	49 1
normal		3	3	1 4
No fever—normal E S R	2	10	12	5 6
No fever, normal E S R and no palpable mass	1	8	9	4 2
Diagnosis "acute salpingitis" clinically probable from the outset	68	74	142	65 7

can be resolved largely by the routine use of laparoscopy Although fears and misgivings have been expressed regarding the performance of laparoscopy in the presence of acute inflammatory conditions in the lower abdominal cavity, we have found no grounds for any such restrictions The method renders possible a correct diagnosis at an early stage which, of course, is also of great advantage from a therapeutic and prognostic point of view Some of the previously held views as to the significance of the various conventional clinical diagnostic criteria must be revised in the light of these laparoscopic findings Of course, careful clinical judgement always is important, but the extreme variability of the clinical manifestations of the disease spotlights the difference between conventional and laparoscopic methods as regards diagnostic accuracy For these reasons it must also be stressed that laparoscopy should not merely be reserved for use in cases of clinically suspected acute salpingitis (*cf* Table II), but that it should be employed on wide indications to achieve maximal effectiveness in detecting cases of acute salpingitis

SUMMARY

A description is given of the routine use of laparoscopy for the diagnosis of acute salpingitis A series of 185 cases seen at the Department of Obstetrics and Gynæcology, Lund, and diagnosed by this means is presented and analysed The clinical manifestations and the diagnosic criteria are reappraised It is concluded that the clinical picture is often so atypical or uncertain that clinical methods of diagnosis alone are unsatisfactory Laparoscopy represents a diagnostic advance and enables an early and accurate diagnosis to be made in the majority of cases The method occasions the patient the minimum of risk and discomfort which is more than outweighed by the many advantages On the basis of our experience we are able to recommend laparoscopy for routine use in the diagnosis of acute salpingitis

This study was supported by a grant from the "Maggie Stephens Stiftelse"

of bacteria Here it is of interest to note that in one of our cases the illness developed immediately after an adequate course of treatment for uncomplicated gonorrhœa There are also good reasons for suspecting that *non-gonorrhœal salpingitis in a proper* sense may sometimes be venereal in origin In the present series such an ætiological mechanism was strongly suspected in over 30 per cent of the 'non-gonorrhœal' cases, both as a result of close personal enquiry and known social factors

In 38 cases bacteriological studies were carried out on material obtained via the laparoscope or via the separately introduced canula (Table VI) Prominent among these were cases with pus or exudate in the pouch of Douglas and cases in which exudate could be aspirated directly from the tubal ostia Neisserian and non-specific cultures were carried out as a routine In addition, in some cases special culture methods were applied for the detection of pleuro-pneumonialike organisms (PPLO), which are assumed by some authors to have a certain ætiological significance in acute salpingitis (cf Melen and Gotthardson, 1955, Lemcke and Csonka, 1962) In 29 of the 38 cases examined (76 per cent), no growth was obtained In the remaining 9 cases, cultures consisted mainly of coliforms, enterococci, staphylococci and streptococci In one case which was pursuing an apparently unremarkable clinical course, a growth of clostridium welchii was reported In only one out of 18 cases of gonorrhœal salpingitis could gonococci be cultured from the tubal secretions In another series published from this department by Sunden (1959) wherein the diagnosis was reached by laparotomy, the incidence of positive bacteriological findings from the pelvis was similarly low Although the present study is too limited in scope to permit of any general conclusions in this respect, it underscores the necessity for further investigations into the bacteriological factors pertaining to acute salpingitis, laparoscopy should prove very useful for this purpose

General conclusions

The diagnostic problems and uncertainties surrounding conventional clinical methods for the diagnosis of acute salpingitis

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EXPERIMENTAL AND CLINICAL STUDIES ON THE FLUOROBIOLOGY OF THE CERVIX[1]

III On a New Cancer Test Basic Considerations[2]

BY

M. SHERIF

MB BCH DGO DS MCH.

Though deoxyribonucleic acid (D N A) and ribonucleic acid (R N A) possess strong affinity to bind planar and semiplanar basic dye cations "*in vitro*" their effective combination with the basic proteins of intact living biological material renders them unstainable by conventional basic dyes (Hammarsten and Teorell, 1928 Michaelis 1947 and others) In common with 3 6 diaminoacridines however the fluorescent basic dye acridine orange was demonstrated to interact with the integrated nucleoprotein complex and to stain *in vivo*" cervical cells of rodents (Sherif 1963 a b c) On excitation with blue violet rays (4040—4360 Å) stained cells would exhibit specific fluorescence spectra determined by the selective binding of the dye cations to nucleic acids of various subcellular compartments In normal living cervical cells whether resting or physiologically active the dye is bound by intranuclear nucleic acids but not by cytoplasmic R N A the fluorescence of such cells would be confined to the nuclei and

[1] The studies are part of A New Cancer Test awarded the Edgar Gentilli prize for the year 1962 and the year 1963 by the Royal College of Obstetricians and Gynæcologists

[2] A lecture delivered at ST Thomas s Hospital Medical School on the 1st of October 1963

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occupy the green spectral range On the other hand, devitalised cells and carcinogen-treated cells would, respectively, exhibit red and yellow cytoplasmic fluorescence which indicate *binding of* acridine cations by cytoplasmic R N A with the formation of two optically different complexes (Sherif, 1963 a, b, c)

In the present report, the results of a study conducted on the tissue level are presented The differential fluorescence of the normal living, the devitalised and the carcinogen-treated mucosa of the mouse cervix is described and the fluorochemistry of the dye-nucleate complexes formed within each of them is discussed Based on the observations reported here and in other works (Sherif, 1963 a, b, c) a new biological test for the clinical detection and localisation of early malignancy is proposed and its basic principles are considered

Material and Methods

A detailed consideration of the methods for application of the carcinogen, devitalisation of the cervical mucosa, parenteral administration of acridine orange and of the optical and fluorescence requirements has already been reported (Sherif, 1963 a, *b*, c)

Thirty C3H mice were treated with 20-methylcholanthrene for a period of 12 to 14 weeks A group of twenty animals were treated with the carcinogen over a longer period (20 weeks) A similar group of animals was kept as a control and a group was treated with weekly *œstradiol injections* over *the same period* In ten of the control animals the cervix was devitalised by thermal or electric cauterisation or by instillation of strong acid into the vagina prior to the administration of acridine orange solution Three hours before examination each animal received a standard dose of 10 mg per kg body weight of acridine orange by one of the parenteral routes, was killed and the uterus and vagina were dissected The cervix was separated from the vagina and cut free at the corporeo-cervical junction with the free hand method utilising a sharp blade Specimens were mounted in a drop of phosphate buffer of pH 6 2, without fixation, examined immediately and their fluorescence compared at low magnification X 20—40 A fluorescence microscope "Ortholux III Leitz" was used with

Philips CS 150 watt mercury high pressure lamp as excitation source and the blue filter BG 12 for the blue-violet range (4040—4360 Å) Photographs were taken on Ektachrome high speed Kodak films by the automatic microscope camera "Orthomat Leitz" The exposure time varied from 0 5 to 2 minutes Examination of all specimens was conducted with constancy of the irradiation intensity irradiation-object distance, temperature pH, and other technical factors

Results

The results of this study can be summarised as follows

1 As judged by the fluorescence, acridine orange stained "in vivo" the intact mucosa of the normal, devitalised and carcinogen treated cervix of the mouse

2 On proper excitation with blue-violet rays (4040—4360 Å) the stained tissues exhibited easily perceptible fluorescence, specific in colour and practically so in intensity for each type of mucosa

3 Normal living cervical mucosa exhibited green uniform fluorescence of moderate intensity (Plate I) Prolonged oestrogen administration neither changed the colour nor affected the intensity of the fluorescence

4 Devitalised mucosa exhibited red fluorescence of low intensity (Plate II)

5 Carcinogen treated mucosa exhibited areas of yellow fluorescence within the green fluorescence of normal mucosa (Plate III) The yellow fluorescence was characteristically, of high intensity and metallic brilliancy and was perceptible as early as seventy two hours after application of the carcinogen

6 With prolonged application of the carcinogen the yellow fluorescence was emitted by wider areas of the mucosa

7 Examination of individual cells obtained from each type of mucosa confirmed the previously reported observations (Sherif 1963 a b)

Discussion

The results of this study will be interpreted in the light of certain observations concerned with modification of the fluorescence

and absorption spectra of acridine orange when bound to nucleic acids (Zanker, 1952 Morthland *et al*, 1954, Bradley and Wolf, 1959, and others), observations on the molecular structure of nucleic acids and synthetic polynucleotides (Astbury, 1947, Wilkins *et al*, 1953, Franklin and Gosling, 1953, Feughelman *et al*, 1955, Rich and Davies, 1956, and others), and the observations reported by the author on acridine orange nucleic acids interaction on the cellular level (Sherif, 1963 a, b, c)

Fluorescence of Normal Living Mucosa

(1) The uniform green fluorescence of normal living cervical mucosa reflected the capacity of intranuclear nucleic acids (mainly D N A) to bind acridine orange cations (Sherif, 1963 a) Uniformity is consistent with the Boivin-Vendrely's concept of D N A constancy in nuclei of normal somatic tissues (Boivin, Vendrely and Vendrely, 1948) Binding of the dye cations by D N A is conceivably established through their competition with the hydrogen ions linking the nitrous bases on the nucleotide plates (Fig 1) The interaction would be favoured by the low energy level of the hydrogen bond which can form and rupture at normal temperatures (Bull, 1950, Pauling, 1960), by the planar configuration of the acridine orange cations (Albert, 1950) and by the large surface which the nucleotides present on the D N A molecule (Feughelman *et al*, 1955) The effective thickness of the aromatic ring of acridine is 3 4 Å, which is in correct order with the internucleotide distance at the fibre axis of D N A (Wilkins *et al*, 1953) However, since the Van der Waals radius of acridine orange cations is 5 5 Å, aggregation of cations would be theoretically and practically impeded and the acridine orange complexes formed with D N A in normal tissues would essentially be monomeric complexes (Zanker, 1952), with a fluorescence peak at the green spectral range (approximately 5400 Å)

The concept which attributes vital staining of intact living biological material with acridine orange and allied 3 6 diaminoacridines to hydrogen-competition mechanism is strongly supported by the reversibility of the staining reaction (Sherif, 1963 c), by the facts that diaminoacridines are less effective, as antibacterials, in

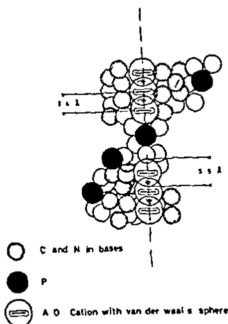


Fig 1 Diagrammatic representation of acridine orange-deoxyribonucleic acid (D N A) interaction in living normal cells and tissues

acidic than alkaline media (Browning *et al* 1919) that their bacteriostasis could be maintained with increase in hydrogen ion concentration if this is balanced by increase in acridine concentration (Albert 1950) and that normal growth of bacteria inhibited by acridines could be restored through the addition of hydrogen carriers (McIlwain 1941)

Fluorescence of Devitalised Mucosa

In living cells and tissues cytoplasmic R N A shows no affinity to bind acridine orange cations since the protein bound phosphate groups would be unaccessible to the dye cations, and since the molecular structure of R N A shortly to be discussed, seems incompatible with a dye base interaction similar to that postulated for D N A (Sherif, 1963 c) Following cellular death and dissociation of the nucleoprotein complex, polar interaction could be

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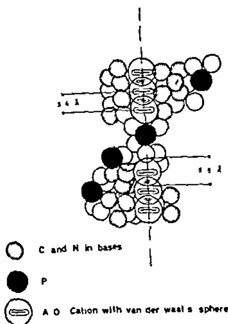


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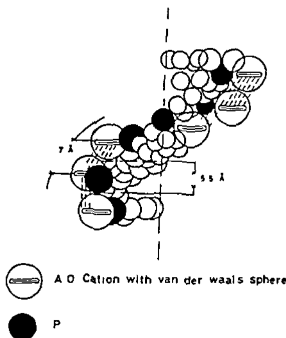


Fig 2 Diagrammatic representation of acridine orange ribonucleic acid (R N A) interaction in devitalised cells and tissues

established between the dye cations and the disengaged phosphate residues along the polynucleotide chain of cytoplasmic R N A (Fig 2) Since the distance between the phosphate residues is in the region of 7 Å (Crick, 1957), and the Van der Waals radius of acridine orange cation is 5 5 Å, extensive cationic aggregation through London dispersion forces would be possible with the consequent formation of polymeric dye complexes which exhibit a fluorescence peak at the red spectral range (approximately 6400 Å) Those optical complexes would neither be dependent on dye concentrations nor modified by them (Michaelis and Granick, 1945), nor would they be subjected to the physicochemical factors which modify formation of similar complexes when acridine orange is bound to nucleic acids in cytologic and histologic preparations (Bertalanffy *et al*, 1956, 1958, and Armstrong 1956) In vitro, cellular fixation would result in depolymerisation of nucleic acids with subsequent alteration in the electrostatic conditions of the molecules (Irwin and Irwin, 1949) while secondary repolymerisation of the acids may favour the formation

of compounds which present, on staining, pure artefacts (Vig, 1956) Further alteration in the molecular electrostatic charges may follow combination of the fixative with ionisable groups and the subsequent precipitation of nucleoproteins Treatment of cells after fixation, the so called "differentiation", may also affect acridine orange-nucleic acid binding (Swift, 1955) Those factors are partially responsible for the unsatisfactory results obtained by various workers (Liu 1956 Elevitch and Brunson, 1961, Anderson and Gunn, 1962 Wied and Manglano 1962) who applied acridine orange as a cytological stain according to Bertalanffy s method (Bertalanffy *et al*, 1956, 1958)

Fluorescence of Carcinogen-Treated Mucosa

The yellow fluorescence of carcinogen treated mucosa reflected the capacity of cytoplasmic R N A to bind acridine orange cations and confirmed the observations on the fluorescence of carcinogen treated cells (Sherif, 1963 b) Emission of the fluorescence at the yellow range of the spectrum at the cellular and tissue levels implies aggregation of the acid bound acridine cations to form in stained cells and tissues optically defined dimeric complexes (Bradley and Wolf 1959) Since R N A of the normal living cytoplasm of a resting or protein synthesising cell exhibits no affinity to bind acridine orange cations (De Bruyn *et al*, 1950, 1953 and Sherif 1963 a c) it is conceivable that an alteration in the molecular structure of R N A is initiated by 20-methylcholanthrene (Sherif 1963 b) Such alteration would not only favour binding of the dye cations but their consequent orientation, in relation to each other, to allow cationic dimerisation An insight could be thrown on this molecular alteration if certain nonidentity could account for the differential capacity of both D N A and R N A of normal living cells and tissues to bind *acridine* orange cations "in vivo" (De Bruyn *et al*, 1950, 1953, and Sherif 1963 a b c) Specificity of both nucleic acids arises from their geometrical configuration and the particular sequence of their constituent residues The first is architectural specificity, the second is chemical specificity, and concerning both little is known in the case of R N A However X ray diffraction dia-

grams of native R N A and some synthetic polynucleotides give a strong impression that R N A exists, like D N A, in two stranded intertwined helices (Franklin and Gosling, 1953 Rich and Davies, 1956, Crick, 1957, Watson, 1957, and Rich, 1957), with the adenine and uracil bases linked by hydrogen bonds as has been postulated for adenine and thymine in D N A by Watson and Crick (1953) Yet this structural homology does not seem to be absolute, since certain differences are recognisable in the X ray diagrams (Rich and Davies, 1956, Rich, 1957) and, in the present state of knowledge, one or more of the following structural characteristics of R N A may account for the inaccessibility of its bases to acridine cations

1 Tilting of the bases in the direction of the pitch of the helix as suggested in polyadenine (Poly A) by the difference between the thickness of purine bases and the fibre axis translation between the nucleotides on a given chain
2 Smaller angular separation of the two ribose-phosphate backbones viewed from the helical axis as compared with the D N A molecule
3 Parallel orientation of the R N A backbones instead of the antiparallel orientation postulated for D N A by Watson and Crick (1953), with the consequent establishment of additional hydrogen bonds

In the light of these considerations, we conceive that the molecular alteration initiated in cytoplasmic R N A by the carcinogen (Sherif, 1963 b) is basically structural and is concerned with an acquired state of molecular flexibility This results in the nucleotide plates assuming optimal positions for the acridine orange cations to approach and strike the nitrous bases Through a hydrogen-competition mechanism, they would establish Van der Waal s forces of sufficient magnitude of energy to fix them in relative orientation compatible with "dimer" formation Since the shortest distance for approachment of two acridines cations is 5 5 Å, a minimal internucleotide distance at the fibre axis of the altered molecule would be in that range which exceeds the internucleotide distance of 3 4 Å demonstrated by crystallography for normal R N A molecule (Rich and Davies, 1956 Watson,

PLATES


Plate I


Plate II


Plate III

1957 and Crick 1957) The fact that the acridine aggregates are formed on the altered molecule in the dimeric form implies random distribution of short dye chains and suggests that the molecular alteration in discussion is irregular rather than regular This would be compatible if model construction is considered with a disorderly folded molecule (Sherif, to be published)

Summation experiments with different carcinogenic agents indicate that a common subcellular stratum is involved in carcinogenesis (Rondoni 1955) and the fundamental significance of an ultrastructural change in the nucleoproteins above that of purely chemical composition was repeatedly emphasized (Powell, 1944, 1947 and Rondoni 1955) The possibility that the nucleic acid molecule could be the primary target for carcinogenic hydrocarbons acting on mouse skin and that subsequent alterations would bring irreversible modification heritable to the cancer cell has also been pointed out recently by Boutwell (1964) while Ceselli and Guzzi (1954) demonstrated through infrared absorption studies a complex modification of the nucleic acids behaviour in tissues during carcinogenesis and emphasized the possibility of a rearrangement at the level of the macromolecular constituents

According to Caspersson (1950) a fundamental difference exists in the protein forming system of the normal and cancerous cell It is very probable in the light of recent observations (Weiss and Nakamoto 1961) that protein synthesis in a normal cell is D N A -dependent and is mediated through the biosynthesis of cytoplasmic R N A which acts as cytoplasmic template for organisation of amino acids (Hoagland *et al* 1959) Yet, to my knowledge no such system of dependency has been demonstrated in a cancerous cell and no specific mechanism of D N A change has yet been described and proved involved in any form of cancer Macrostructural abnormalities such as chromatin irregularity and the like in a cancer cell are unlikely to be causally connected with tumour induction and propagation but rather associated relatively advanced secondary changes (Haddow 1951) On the other hand the investigations of Ledoux (1955) on the effect of ribonuclease on mouse tumours "in vivo" would favour the existence of an altered cytoplasmic R N A molecule that may act as an

(1962) who demonstrated that leukaemic R N A can induce, in normal human amnion cells, the production of proteins with different antigenic determinants in comparison to those produced in similar cultures inoculated with R N A from normal sources As regards the characteristic dedifferentiation of the cancer cell there is considerable evidence from studies of transplantation of nuclei from amoeba, that differences between differentiated cell types are produced and maintained by changes in the cytoplasm (Lorch and Danielli 1950)

Variations in the Fluorescence Intensity

Though the acridine nucleic acids complexes described in this work were fairly identifiable by their different spectral ranges, variations in intensity were constantly observed and are worthy of special consideration Concerning the high intensity of the fluorescence of normal tissues in comparison with that of devitalised tissues, it is recognised that in term of relative intensity on molar bases the 5400 Å fluorescence maximum is in the order of 8—10 times as brilliant as that at 6400 Å This is due to considerable quenching of the intensity of fluorescence emission of acridine orange nucleic acids complexes as the extent of complexing is increased Low intensity fluorescence of devitalised tissue would be also due to the quenching effect of free nucleic acids since it is demonstrated that fluorescence quenching is less evident when nucleic acids are bound to proteins (Oster, 1951)

Carcinogen treated cells and tissues exhibit high intensity fluorescence in comparison to other tissues since the fluorescence complexes are formed between the dye and cytoplasmic R N A and it is recognised that the quenching constant[1] of R N A is much more lower than that of D N A (Oster 1951)

THE NEW CANCER TEST

In 1941 Robert Mayer stated that "the morphological changes which have been demonstrated as characteristic of very early cer

[1] The quenching constant is a function of the probability of quenching at an encounter between the dye and the quenching molecules the sum of the radii of the quencher and the dye and the life time of the fluorescence of the dye

abnormal template for production of cancerous proteins (Brachet 1957) and, according to Rondoni (1955), the despecialisation of those proteins is likely to result from a change in the shape, the internal configuration and the folding specificity of the molecule

A structurally abnormal, self-dependent, protein-forming system in the cytoplasm of the cancerous cell could account for the autonomy in synthesis of these proteins, their altered structure, and their abnormal biological functions (Sherif, to be published)

As regards the possible mechanism through which 20-methyl cholanthrene would initiate intramolecular alteration in R N A, various authors have suggested that an aromatic hydrocarbon molecule, planar as it is, could fit within the helical structure of cellular macromolecules and that this is an important factor in carcinogenecity (Arcos and Arcos, 1955, Haddow, 1957, Huggins and Yang, 1962, and others) Whether the molecular *alteration of R N A postulated in our work is due to a critical* spacial configuration of the carcinogen molecule, to its overall electronic configuration or to a specific reactive feature which would change, through breaking or formation of certain bonds, a well defined fairly rigid molecular architecture into a flexible less orderly structure is a question for further consideration (Sherif, to be published) and the same applies to changes in chemical specificity that may follow configurational alterations However, since the acridine orange-nucleic acids interaction, in advanced animal and human neoplasms "in vivo", would lead to formation of dimeric complexes similar to those described in this study *(Sherif, 1963 c), there is reason to believe that the ab*normal molecule is capable of genetic transformation of the cancer trait from a mother to a daughter cell *Certainly no definite* complementary structure as that described for D N A by Watson and Crick (1953), is recognised at present for R N A, yet this is conceivable since replication of R N A at the molecular level is strongly suggested by the experimental observations on the process of infectivity of tobacco mosaic virus (Fraenkel Conrat, 1957) and meningoencephalitis virus (Schramm and Gierer, 1957) That the altered R N A molecule could act as a three dimensional template for synthesis of specific cancerous proteins is evidenced by the work of De Carvalho and his associates

reported in this study and in previous works (Sherif, 1963 b c) point to a key molecular event in the initiation of cervical cancer, and the possibility that the molecular change resulting in an initiated cancer cell would occur spontaneously at low frequency during nucleic acid reduplication has been emphasized (Sherif 1963 c Boutwell 1964)

The question of early cancer detection in the opinion of the author of this work would be the question of recognition of this phase of biological latency through the objective perception at the tissue level of those molecular changes In the cervix uteri, and other accessible human organs this could be achieved clinically through

A Vital staining with acridine orange
B Excitation and inspection of the stained organs "in situ" by specially constructed intravital fluoromicroscopic optical systems which utilise the blue-violet rays *in the region of* 4040—4360 Å[1] (Sherif, 1963)

The basic aim of this test would be to identify various acridine orange-nucleic acids complexes formed "in vivo" by virtue of their differential fluorescence and to detect and localise, consequently early malignant transformations in a biological sense

The potentiality of the test would be augmented by the high sensitivity of the fluorescence techniques which exceeds, theorecally and practically that of conventional staining *methods* and absorption techniques which are limited by finite molar extinction Fluorescence would additionally provide high contrast by low concentration of dyes which would *not* interfere with physiologic tissue behaviour The technique applied to living biological material would be entirely devoid of distribution error and fixation artefacts (Price and Schwartz 1956) I am not unaware, however that the diagnostic potentiality of this test would be limited to surface lesions yet it is recognisable that the earliest changes consistent with neoplasia occur as surface changes in the cervix uteri and probably in other human organs (Broders,

[1] Optical systems for detection and localisation of early cancer of accessible human organs according to this test are manufactured by J D Moller Optic Works Wedel—Hamburg Western Germany

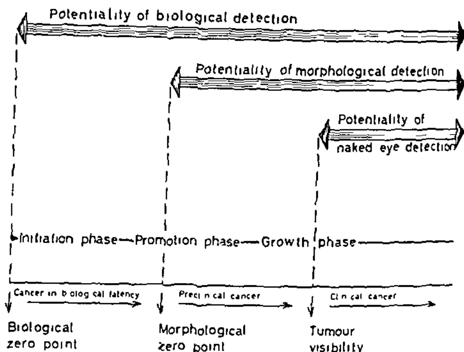


Fig 3 The comparative potentiality of cancer detection methods

vical cancer are already far advanced in terms of theoretical onset of the cancerous change in the cell" Recent progress in experimental carcinogenesis has indicated that cancer originates as a series of biological changes which involve basically two steps, an "initiation phase" characterised by specificity, apparent speed of action and irreversibility, and a gradual nonspecific "promotion phase" which would eventually culminate in morphologically recognisable malignancy (Friedwald and Rous, 1944, Berenblum, 1954 Rusch and Kline, 1946, and others) Experimentation with interrupted carcinogenic agents (Lavik *et al*, 1942, Des Ligneris, 1940, Berenblum and Shubik, 1949, Rusch and Kline, 1948, and others) indicates that the initiated biological changes could be promoted after a considerable period of latency by non-carcinogenic agents

Paucity of knowledge concerning this phase of biological latency (Fig 3) has been basically due to limitation of methodology (Berenblum, 1944, Busch, 1962, and others) The observations

SUMMARY

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I wish to acknowledge my deep gratitude and indebtness to Professor A Ingelman Sundberg M D, for his unfailing help, interest and encouragement My thanks are due to Mr A J Wrigley F R C O G, for the kind invitation to deliver this lecture to Professor E Navratil M D (Graz), to Professor H Sobhi, F R C S (Egypt) for their stimulating interest, and to Docent M Furuhjelm M D, for the permission to carry on the experiments at Sabbatsberg s Hormone Laboratorium

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1932, Willis, 1953, and others) The rare monophasic spray carcinoma of the cervix which starts from the basal cells (Schiller et al, 1953) seems to have no practical significance, and identical varieties reported by other authors (Limburg, 1956, and Mestwerdt, 1957) do not seem to have bearing on the cervix

Conclusions

1 The fluorescent basic dye acridine orange (3 6 bis-dimethylaminoacridine) stains "in vivo" normal, devitalised, and carcinogen treated mucosa of the mouse cervix
2 Three optically-defined complexes are formed between the dye cations and nucleic acids They are identifiable by virtue of their differential fluorescence when excited by blue-violet waves (4040—4360 Å)
3 In normal living mucosa dye complexes are formed with intranuclear nucleic acids (mainly D N A), are essentially monomeric and emit green fluorescence of moderate intensity
4 In devitalised mucosa dye complexes are formed with the freed cytoplasmic R N A , are essentially polymeric and emit red fluorescence of low intensity
5 In carcinogen-treated mucosa dye complexes are formed with cytoplasmic ribonucleoproteins, are essentially dimeric and emit yellow fluorescence of high intensity Conceivably, a specific architectural alteration in the internal configuration of the R N A molecule, consequent on the action of the carcinogen, underlies the formation of those particular complexes
6 Identification of the intramolecular changes of cytoplasmic R N A can be achieved, at the tissue level, through vital staining with acridine orange and the application of *intravital* fluoromicroscopic instruments utilising for excitation the blue-violet rays (4040—4360 Å)
7 This combination is proposed as a new test for recognition and localisation of early malignancy of the cervix as well as other accessible human organs

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From the Department of Obstetrics and Gynæcology (Professor Ernst Schjøtt Rivers) Rikshospitalet Oslo Norway

RECOVERY FOLLOWING SURGICAL OPERATION DURING PREGNANCY

BY

ODDMUND KOLLER

Surgical operation on a pregnant woman may endanger the health and life of the fœtus If the operation results in abortion or premature labour the risk for the mother also is increased Changed anatomical and physiological conditions, such as increased vascularity may also contribute to higher rate of complications Montgomery (1952), dealing with surgical problems in obstetrics writes Because of the extreme vascularity of the parts operation is more hazardous Such procedures as myomectomy are particularly hemorrhagic and even the removal of an ovarian cyst may be associated by far more than the ordinary amount of blood loss Vascular pedicles have to be secured with extreme care "

On the other hand there is clinical evidence that the healing capacity of the pregnant organism is improved compared with that of the non pregnant woman Sjovall (1948) states that, in the absence of infection puerperal wounds, perineal ruptures, episiotomies etc heal with astounding rapidity Von Haller (1953) referring to the similarities in the physiology of the growing child and the pregnant woman found children *and pregnant* women to stand operative trauma better than non pregnant *adults* There is however, a lack of clinical documentation to support these statements

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Working as a staff member at the Department of Obstetrics

and Gynæcology, Rikshospitalet, Oslo, the author was impressed by the strikingly smooth recovery in pregnant women subjected to different types of gynæcological surgery The present study was undertaken to test the validity of this clinical impression. The investigation was planned and performed during the years 1952 to 1956, but the publication has for several reasons been postponed

Material

The study is based on the Hospital Records of the gynæcological department, Rikshospitalet, from the years 1945—1954 and comprises all operations performed in pregnant women where control cases of non-pregnant women subjected to similar operations were available All cases of curettage for interruption of pregnancy were excluded as this is obviously an operation quite different from curettage in the non-pregnant women Neither could comparable operations be found in non pregnant women for termination of pregnancy by abdominal hysterotomy, nor for operations performed in cases of ectopic pregnancy and for cases with incarceration of the pregnant uterus in the pelvis Sixty-six pregnant women with 165 non-pregnant control patients were included in the study

To provide for a statistically valid control material the following procedure was applied

The records were reviewed chronologically When a certain type of operation on a pregnant woman was registered, all succeeding cases of the same operation in non-pregnant women, except when excluded as described below, were used as control cases The available number of cases of subtotal hysterectomy was so great that only a random sample was used

In order to exclude as far as possible other causes for postoperative reaction than the specified surgical interventions, the following patients were not accepted as controls

1) Patients in which surgery additional to the primary procedure had been undertaken or in which bladder or bowel had been accidentally opened during the operation Cases in which myomectomy involved opening the uterine cavity were excluded

2) Patients with previous operations on the genital organs which may influence

the character of the present operation Previous subtotal hysterectomy for example may change the anatomical and physiological conditions in such a degree that a salpingo-oophorectomy in this patient is not comparable to a similar operation on an individual with intact genital organs Similarly removal of one ovary from a patient previously subjected to unilateral ovariectomy would result in castration with far reaching effect upon the organism Obviously this operation could not be compared with a unilateral oophorectomy in a woman with two functioning ovaries

3) Patients where pregnancy could not be definitely diagnosed or excluded and patients who presented signs of abortion prior to the operation

4) Patients with acute or chronic genital or extragenital infections present or likely to be present at the time of the operation

5) Patients with extensive adhesions or intraligamentary tumours which made operation difficult to perform

6) Patients where the diagno is of endometriosis could be established on reasonable clinical or pathologic anatomical evidence This was done because endometriosi perhaps may be a revelation of a special type of peritoneal reaction which may also be reflected in the reaction to trauma Many of the endometriosis cases also presented extensive adhesions

7) Patients with a high degree of obesity

8) Patients with diabetes mellitus

9) Patients with heart failure renal disease or with hypertension causing symptoms

10) Patients with malignant growths

11) Patients with insufficient or obscure information

Results

Table I shows the selected material in pregnant and non-pregnant groups according to the type of operation All operations were performed by equally experienced qualified members of the staff

The duration of the pregnancy at the time of operation is shown in table II

The age distribution (table III) was relatively similar in the pregnant and non pregnant groups In operation groups B and C all non pregnant women were within the reproductive age Group A however contains one prepubertal girl and 4 post-menopausal women

Anæsthesia General anæsthesia with ether or nitrous oxide was used in all cases except for one pregnant and one nonpregnant patient who both had local infiltration anaesthesia In 3 of the

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Table III

Types of Operation		Age Groups 15–19	20–24	25–29	30–34	35–39	40–44	45–49	50–54	55–59
Group A	Pregnant	1	3	8	13	9	5	0	0	0
	Non pregnant	2	14	13	33	22	9	5	1	2
Group B	Pregnant	0	0	0	2	1	14	1	0	0
	Non-pregnant	0	0	0	3	10	34	10	2	0
Group C	Pregnant	0	3	3	0	2	1	0	0	0
	Non pregnant	0	0	1	0	2	2	0	0	0
Total	Pregnant	1	6	11	15	12	20	1	0	0
	Non pregnant	2	14	14	36	34	45	15	3	2

pregnant and in 10 of the non pregnant patients a muscle relaxant was also administered

The abdominal incisions in the pregnant groups were of the low midline type in 59 cases, of the low transverse in 2 and of the McBurney type in 4 cases (appendectomy) In the nonpregnant group 162 had low midline incisions and 2 low transverse incisions

Sulphonamides and antibiotics were given more frequently in the pregnant than in the non pregnant group, 18 2 compared with 12 7 per cent When only prophylactic administration is considered, however, the difference is small, 7 6 compared with 6 7 per cent

Group A In *operations on the adnexæ*, comprising 17 pregnant and 62 non pregnant cases, the sizes of the cysts were similar in the pregnant and the non pregnant group No tumours of the hormone producing type were diagnosed on histological examination

The operations on the uterus comprising 22 pregnant and 39 non pregnant cases were all myomectomies The myomas removed were considerably larger in the pregnant than in the nonpregnant groups 7 of the myomas in the former but none in the latter being the size of a fœtal head at term or more The average number of myomas removed in the pregnant series was 2 2 and in the non pregnant series 2 7 In the pregnant group the

Table I

	Types of Operation	Number of Pregnant Women	Number of Non-Pregnant Women
Group A (Operations on the internal genital organs compatible with the preservation of a pregnancy)	Unilateral excision of ovarian cyst(s) or resection of one ovary	3	15
	Bilateral excision of ovarian cysts or resection of both ovaries	1	3
	Unilateral oophorectomy	8	18
	Unilateral salpingo oophorectomy	4	22
	Unilateral excision of parovian cyst	1	4
	Myomectomy	22	39
	Total	39	101
Group B (Operations on the internal genital organs not compatible with the preservation of a pregnancy)	Subtotal hysterectomy	12	42
	Subtotal hysterectomy and unilateral salpingo-oophorectomy	6	17
	Total	18	59
Group C (Operations outside the genital tract)	Exploratory laparotomy	4	2
	Hernioplasty	1	1
	Appendectomy	4	2
	Total	9	5
Total		66	165

Table II

Types of Operation	Duration of the Pregnancies in Weeks 5–8	9–12	13–16	17–20	21–24	25–28
Group A	4	16	11	4	4	0
Group B	3	9	6	0	0	0
Group C	0	4	3	0	1	1
Total	[illegible]	[illegible]	[illegible]	[illegible]	5	1

surement of the rectal temperature twice daily, at 7 a m and 4 p m Temperatures of 38° or more are listed as fever and are detailed in tables IV V and VI

The tables reveal that in all types of operations the incidence of fever was consistently lower in the pregnant than in the non-pregnant group Overall the difference is statistically highly significant ($p<0.0005$ by the chi square test) In addition the fever tended to be lower and of shorter duration in the pregnant patients Among the 11 types of operation there were only 2 exceptions the unilateral salpingo-oophorectomy and the sub-total hysterectomy groups A detailed examination of the record of the affected patient in the former group indicated that the fever in this case was a side effect of intravenous fluid administration

Further analysis of the postoperative course (abortion excluded) is given in table VII

In all main operation groups the incidence of uneventful recoveries was higher and of postoperative complications lower in the pregnant compared with the non pregnant cases This holds for fever as well as for "other complications" The differences are statistically highly significant ($p<0.0005$) in relation to uneventful recoveries and to fever as the sole complication The difference however for "other complications", is not statistically significant

Table VIII shows the diagnoses included in "other complications" and the distribution of these diagnoses between the pregnant and the non pregnant patients The table reveals that all complications of infectious type (20 cases) occurred among the non pregnant patients This difference is statistically significant at a level of $0.025>p>0.010$

Hæmatomas were not conspicuously more frequent in the pregnant group

The only 2 cases of gastro-intestinal paresis occurred in pregnant patients Both were severe and long standing but responded to conservative therapy A second laparotomy did not become necessary

incidence of intramural myomas was 71 per cent and the incidence of subserous or pedunculated myomas 29 per cent, compared with 78 per cent and 32 per cent in the non-pregnant group.

Group B. All pregnant and all except 6 non-pregnant patients had uterine myomas. In the latter 6 cases the main indication for surgery was metrorrhagia. In most cases if the adnexa were removed it was for technical reasons. Histological examination did not reveal any tumours of the hormone-producing type.

Group C. Two of the four pregnant patients subjected to *exploratory laparotomy* were operated because of suspicion of ectopic pregnancy, but the operation showed apparently normal pregnancy. In the remaining 2 cases the pregnancies were associated with myomas. The preoperative diagnosis in the non-pregnant patients was in both cases retroflexion and fixation of the uterus associated with pelvic pains. In one case the operation revealed normal genitalia and in the other such extensive adhesions that the operator abstained from further surgery.

The herniaplasty in the pregnant patient was for an inguinal hernia and in the non-pregnant case for a femoral hernia.

In *the appendectomy group* appendicitis had been suspected because of pelvic pains in all but 1 case. This case was a non-pregnant woman where the indication for laparotomy was sterility, probably because of obstructed tubes. At operation, however, the genitalia were found to be of normal appearance and with patent tubes. None of the cases presented histological signs of acute or subacute inflammation of the appendix.

The postoperative complications

The overall *abortion rate* following operation performed with the intention of preserving pregnancy (Groups A and C) was 23 per cent. Operations outside the genital tract resulted in 17 per cent, operations on the adnexa in 18 per cent and operations on the uterus in 32 per cent of abortions. Some of the pregnant patients had received progesterone therapy to try to prevent abortion. The doses, administered, however, were very small.

The postoperative *temperature reaction* was followed by mea-

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Table IV *Operations of Group A*

Types of Operation	Pregnant Women				Non Pregnant Women			
	Total	Number of Febrile Cases	Average Number of Times Fever Recorded in the Febrile Cases	Max. Temperature Registered	Total	Number of Febrile Cases	Average Number of Times Fever Recorded in the Febrile Cases	Max. Temperature Registered
Unilateral excision of ovarian cyst(s) or resection of one ovary	3	1	1 0	38 0°	15	15	2 9	39 0°
Bilateral excision of ovarian cysts or resection of both ovaries	1	0	0	—	3	3	4 7	38 4°
Unilateral oophorectomy	8	2	1 0	38 0°	18	17	4 0	38 8°
Unilateral salpingo oophorectomy	4	1	5 0	38 9°	22	19	4 1	38 7°
Unilateral excision of parovarian cyst	1	0	0	—	4	3	2 0	38 2°
Myomectomy	22	13	2 2	38 7°	39	38	5 2	39 1°
Total	39	17	2 2	38 9°	101	95	4 2	39 1°

Table V *Operations of Group B*

Types of Operation	Pregnant Women				Non-Pregnant Women			
	Total	Number of Febrile Cases	Average Number of Times Fever Recorded in the Febrile Cases	Max Temperature Registered	Tot l	Number of Febrile Cases	Average Number of Times Fever Recorded in the Febrile Cases	Max Temperature Registered
Subtotal hysterectomy	12	11	6 1	38 8	42	42	5 1	39 0°
Subtotal hysterectomy and unilateral salpingo-oophorectomy	6	3	6 0	38 5	17	16	6 1	38 9°
Total	18	14	6 1	38 8	59	58	5 4	39 0°

Table VI *Operations of Group C*

Exploratory laparatomy	4	0	0	—	2	0	0	—
Hernioplasty	1	0	0	—	1	1	5 0	39 1°
Appendectomy	4	0	0	—	2	2	2 0	38 2
Total	9	0	0	—	5	3	3 0	39 1

Table VII *Postoperative Course (Abortions Excluded)*

Types of Operation	Number of Pregnant Women (Per Cent in Parenthesis)			Number of Non-Pregnant Women (Per Cent in Parenthesis)		
	Fever Only	Other Compl	No Compl	Fever Only	Other Compl	No Compl
Group A	14 (35 9)	4 (10 3)	21 (53 0)	78 (77 2)	19 (18 8)	4 (4 0)
Group B	12 (66 7)	2 (11 1)	4 (22 2)	48 (81 4)	10 (17 0)	1 (1 7)
Group C	0 (0 0)	0 (0 0)	9 (100 0)	2 (40 0)	1 (20 0)	2 (40 0)
Total	26 (39 4)	6 (9 1)	34 (51 5)	128 (77 6)	30 (18 2)	7 (4 2)

Table VIII

Other Complications	Number of Pregnant Women	Number of Non Pregnant Women
Pulmonary infections	0	12
Urinary infections	0	6
Infections of the wound	0	2
Hæmatomas	2	4
Gastro intestinal paresis	2	0
Deep thrombosis of the lower extremity	1	4
Pulmonary embolism	1 (a)	1 (b)
Acute exanthema	0	1
Total	6	30

(a) Occurred in a patient with mitral stenosis
(b) The only fatal complication in the series

Discussion

In the present study of pregnant and non-pregnant women subjected to similar types of gynæcological operations, uneventful recoveries (abortions excluded) were significantly more frequent in the pregnant group The difference was mostly due to the conspicuously low postoperative temperature reaction of the pregnant patients ($p < 0\ 0005$)

Seulberger Doring and Peters (1952) found the average postoperative temperature lower in females than in males, and with increasing age the patients were less prone to develop fever According to the same authors this reduced tendency to develop fever is associated with a reduced resistance of the organism and an increase of the postoperative complications

The data presented in this study do not indicate that the low temperature reaction in pregnant women is associated with reduced resistance of the organism The opposite interpretation seems more likely, as indicated by the frequent uneventful re coveries and the low rate of complications other than fever in the pregnant group The difference as to the "other complications" however was not statistically significant

If only postoperative infections are considered however, the difference between the pregnant and the non pregnant group is statistically significant ($0.025 > p > 0.010$) This fact seems to support the assumption of increased resistance of the pregnant organism

A detailed study of "other complications" also revealed other interesting facts There were no reports of excessive bleeding, and postoperative hæmatomas were not more frequent in the pregnant group These data of course must not be interpreted as indicating that the risk of bleeding is negligable but rather that this may be practically eliminated by good surgical technique

The severe gastrointestinal paresis which developed in 2 pregnant patients may be just a coincidence It may however, be related to the pregnant state preconditioned by the pressure, dislocation and the relative atonicity of the intestines

Sjovall (1948) stressed that the rich vascularization of the tissues was probably an important factor in providing locally favourable conditions for healing processes in pregnancy and this might primarily be due to the large amount of *œstrogen* present in the pregnant organism He demonstrated that the healing of experimental vaginal wounds in spayed rats is promoted by the administration of œstrogen Increased vascularization of the genital tract may account for the smooth recovery after operations on the adnexæ and on the uterus in pregnant women demonstrated in the present study Neighbouring areas in the

lower abdomen (abdominal wall, femoral and inguinal region) may perhaps also benefit from this increased genital vascularization As shown in table VIII, however, infections of the respiratory and urinary tract are also less frequent in the pregnant than in the non-pregnant group This seems to indicate a more generalized increase of resistance There are experimental investigations to support such findings Meyer, Stucki and Aulsebrook (1953) in a study on rats demonstrated that pregnancy and lactation markedly reduced the formation of granulation tissue induced by subcutaneously implanted cotton pellets, and also protected the synovial membrane of the knee joint against the injurious effect of formaldehyde These phenomena were believed to be due primarily to an increase in the glucocorticoid moiety of the unique complex of interacting steroids existing during pregnancy and to a less extent during lactation

Our data as to the influence of pregnancy on the healing processes and the mechanisms responsible are still very incomplete Further research is warranted, not only from a purely theoretical point of view, but also because the results may become of practical clinical significance A hormonal state similar to pregnancy can be induced by medication The importance of œstrogen administration prior to operations for prolapse in elderly women seems to be well established (Bourne and Williams, 1945, Sjövall, 1948) Cramer, Hertz and Young (1952) administered progesterone preoperatively to facilitate radical operation for cervical cancer It may be that appropriate hormonal therapy could become an useful adjunct to surgery also outside the pelvic-genital area and in all age groups

SUMMARY

The present study was undertaken to test the validity of the clinical impression that, apart from incidental abortions or premature labours, pregnant women had a strikingly smooth postoperative recovery

The study is retrospective and based on the Hospital Records of the gynæcological department, Rikshospitalet, from 1945 to 1954 The material comprises all operations performed in preg-

nant women—66 cases—where control cases of non-pregnant women subjected to similar operations were available The 165 control cases were carefully selected in order to provide statistically valid material The types of operations are listed in table I

In all 3 main operation groups the rate of uneventful recoveries was higher and the rate of postoperative complications lower in the pregnant compared with the non pregnant group The difference was statistically highly significant ($p < 0.0005$) as to the incidence of uneventful recoveries and to the incidence of cases with fever as the sole complication The difference, however, was not statistically significant for "other complications" (table VII)

The diagnoses included in "other complications" are given in table VIII which reveals that all complications of infectious type (20 cases) occurred among the non pregnant patients This difference is statistically significant at a level of $0.025 > p > 0.010$

Based on these findings the question of hormonal therapy as an adjunct to surgery is discussed

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FURTHER OBSERVATIONS ON THE URINARY EXCRETION OF HISTAMINE DURING AND AFTER NORMAL PREGNANCY

BY

T BJURÖ S LINDBERG AND H WESTLING

In a previous paper we reported some observations on changes in blood and urinary histamine during the last weeks of normal and pathological pregnancies, and in the puerperium (Bjuro, Lindberg and Westling, 1961) The main purpose of the present report is to describe similar changes occuring in the earlier stages of pregnancy, and the effect of aminoguanidine upon the urinary excretion of histamine In addition a few observations on the urinary excretion of 5-hydroxyindoleacetic acid are reported

Methods

The methods used for determinations of blood and urinary histamine (Duner and Pernow, 1956), as well as other pertinent methodological details, are reported in the previous paper (Bjuro *et al*, 1961) The urinary excretion of free histamine is given as μg histamine base excreted in 24 hrs

Aminoguanidine sulphate (Eastman Kodak) was given in a dosage of 50 mg 4 times daily by the mouth This dosage has been shown to inhibit histaminase completely (Lindell, Nilsson, Roos and Westling, 1960)

The urinary excretion of 5 hydroxyindoleacetic acid (5 HIAA)

Table 1 *Urinary Histamine Levels in Early Pergnancy in 14 Women*
Mean values for the urinary excretion of histamine during 2-4 days are given together with the extreme values Figures denote µg free histamine base excreted in 24 hours

10th 13th Week			14th-17th Week		
Case no	Mean value	Range	Case no	Mean value	Range
4	17	6- 27	1	58	23-99
5	36	17- 81	2	25	11-57
7	40	26- 53	3	23	7-40
9	53	23- 82	6	56	46 66
10	21	14- 28	8	23	9-40
11	55	23-110	10	27	18-33
12	7	3- 14	12	13	9-18
			13	33	19-59
			14	61	107 15

Normal value in non pregnant women 12 5 ± 2 0 µg/24 hours S D 6 9



Fig 1 Urinary excretion of histamine in µg 24 hrs (vertical bars) during normal pregnancy Note rising values towards parturition (P) The normal mean value and the upper normal limit (Mean + 2 × S D) are indicated

is given in mg/24 hours 5 HIAA was determined in the same urine specimens as used for histamine estimations The determination was made essentially as described by Udenfriend, Titus and Weissbach (1955)

Material

Studies were made on eleven women (Cases 1–9, 13 and 14), who were in the 3rd to 4th month of pregnancy and on whom legal abortion was later performed for psychiatric reasons In addition measurements of the urinary histamine were made on three women with normal pregnancies (Cases 10, 11 and 12), in these women the urinary excretion of histamine was followed at intervals from the 9th week throughout the whole of pregnancy Aminoguanidine was given to five of the pregnant women (Cases 6, 8, 9, 13 and 14) who were going to have legal abortion and to three healthy, non-pregnant women

Results

Table I shows the mean values for the urinary excretion of histamine in early pregnancy It will be seen from the table that slightly over half of the pregnant women had a mean urinary histamine level which exceeded the upper normal range previously obtained in non pregnant women (12.5 ± 2.0 µg/24 hours, standard deviation 6 9) by Bjuro *et al* (1961)

The course of the urinary histamine excretion during pregnancy in a normal woman is shown in Fig 1 It will be seen that a definite trend towards higher values develops in the middle part of pregnancy The highest value recorded is on the day before parturition, thereafter the values return to the normal level except for a single high value on the fourth day after delivery

It was thought to be of interest to examine the effect of aminoguanidine (a powerful histaminase inhibitor) on the urinary excretion of free histamine during pregnancy Urine was collected for 2–3 days before and for 2 days during the administration of aminoguanidine sulphate in five pregnant women and three controls It will be seen from Table II that aminoguanidine had no definite effect on the urinary output of histamine in either group The values were, however, rather variable in the pregnant group and a small effect of aminoguanidine cannot be excluded The administration of aminoguanidine apparently had no untoward effects on the mothers or fœtuses

Table II Effect of Aminoguanidine on the Urinary Excretion of Free Histamine in 5 Pregnant and 3 Non Pregnant Women

Urine was collected for 2 3 days before and for 1 2 days during the administration of aminoguanidine sulphate 50 mg 4 times daily by mouth.

Case	Age (Years)	Duration of Pregnancy (month)	Urinary Histamine µg 24 Hours				
			Before Aminoguanidine			During Aminoguanidine	
6	18	IV	—	66	46	106	70
8	20	III IV	27	9	17	23	19
9	34	III	82	23	55	71	49
13	27	IV	59	19	20	24	100
14	38	IV	—	107	15	57	—
Controls (non pregnant)							
1	32	—	9	12	16	15	18
2	33	—	3	2	2	2	3
3	30	—	4	3	9	4	2

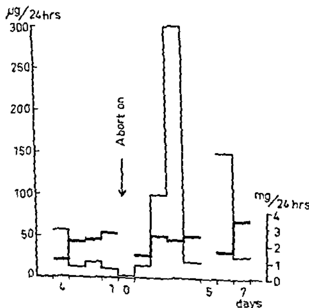


Fig 2 Urinary excretion of histamine (thin lines left scale) and 5 hydroxyindoleacetic acid (thick lines right scale) before and after surgical interruption of pregnancy

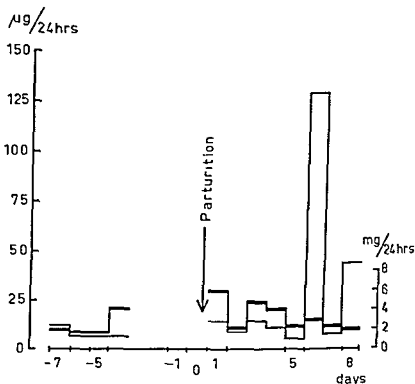


Fig 3 Urinary excretion of histamine and 5 hydroxyindoleacetic acid before and after parturition For explanations see Fig 2

Previous observations have shown that there occurs after normal delivery a brief but pronounced elevation of the urinary histamine level (Bjuro *et al*, 1961, Lindberg and Westling, 1961) This phenomenon was also seen in the present series (Fig 1) Fig 2 shows similar observations on the urinary histamine after surgical abortion In addition to histamine values, observations on the urinary excretion of 5 HIAA are given It will be seen that the excretion of histamine was considerably raised after abortion, without a corresponding change in the output of 5-HIAA Fig 3 shows similar observations after normal pregnancy No increase in the urinary output of 5 HIAA occurred at the 6th day after delivery, when a conspicuously high histamine value was recorded

Discussion

The results of the present study suggest that during early preg nancy there is sometimes an increased output of histamine into the urine just as in normal pregnancy near term The possible origin of this histamine has been discussed (Bjuro *et al*, 1961) The increase in urinary histamine during human pregnancy is small in comparison with that in the pregnant rat (Kahlson, Rosengren and Westling, 1958) or mouse (Rosengren, 1963) Strong evidence has been obtained that large amounts of histamine are produced in rat and mouse fœtuses in the uterus (Kahlson Rosengren, Westling and White, 1958 Rosengren 1963) In man such evidence is meagre Admittedly human fœtal tissues can produce histamine *in vitro* (Lindberg, Lindell and Westling 1963 b) but the rate of formation is comparatively small In addition it should be remembered that histamine formed in the tissues and delivered to the fœtal blood will be practically completely metabolized before it reaches the mother s urine after passing the placenta the mother s plasma and kidneys all of which possess powerful histamine-inactivating enzymes (Lindberg Lindell and Westling 1963 a)

An examination of the effect of aminoguanidine on the urinary histamine in human pregnancy might give valuable information since this substance is a powerful histaminase inhibitor (Schuler, 1952) also in man (Lindell *et al* 1960) and increases the urinary histamine in the pregnant rat (Kahlson *et al*, 1958) In view of the importance ascribed to histaminase in plasma and placenta in the pregnant woman (*e g* Swanberg 1950) it would seem likely that an increased production of histamine in the fœtus (or elsewhere) could be revealed by a large increase in the urinary histamine in the pregnant woman under the influence of aminoguanidine Contrary to expectation, aminoguanidine had no measurable effect on the urinary histamine in the pregnant women just as in non pregnant subjects (Mitchell 1956 and the present study) The lack of effect of aminoguanidine in pregnant subjects may be explained by assuming that the urinary histamine has been formed in the kidney and excreted directly without being exposed to histaminase Another perhaps

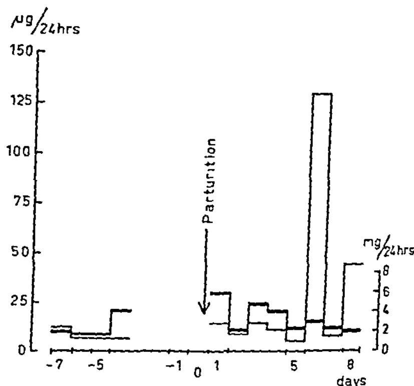


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more likely explanation is based on the observation (Lindberg *et al*, 1963 a) that ^{14}C-histamine injected into the umbilical artery of the living human fœtus is metabolized preferentially by methylation before it reaches the mother's urine This being so, aminoguanidine cannot be expected to decrease the rate of inactivation of histamine formed in the fœtus and delivered to the mother

It seems likely that the final evidence for or against histamine formation in the human fœtus *in vivo* will not be obtained until methods are available for measuring the metabolic products of endogenous histamine, particularly methylimidazoleacetic acid (c f Lindberg, 1963) Theoretically, some information could be gained from experiments with ^{14}C-labelled histidine, but the administration of this substance to fertile women does not appear justified at present

The cause of the brief elevation in urinary histamine after delivery has been discussed previously (Lindberg and Westling, 1961) It was thought to be of interest to see whether the observed changes in the urinary excretion of histamine were accompanied by changes in the excretion of 5-hydroxyindoleacetic acid since there are sometimes simultaneous changes in the release and urinary excretion of histamine and 5-hydroxytryptamine both in animals (*e g* Lewis, 1958) and in man (Pernow and Waldenstrom, 1957) It will be seen from Figs 2 and 3, that the increase in urinary histamine seen after surgical interruption and after normal delivery was not accompanied by any changes in the urinary output of 5-HIAA

SUMMARY

In 9 out of 14 women in early pregnancy (10th–17th week) abnormally high values for free histamine in the urine were observed

Aminoguanidine, a histaminase inhibitor, did not increase the urinary histamine levels

There were no obvious changes in the urinary excretion of 5-hydroxyindoleacetic acid after normal delivery or surgical interruption of early pregnancy

Technique

Fœtal electrocardiograms are obtained by means of

a) a fœtal electrode serving as pick up unit, and

b) a recorder

Two types of fœtal electrodes have been designed, the first of these, called the agraffe electrode, is depicted in Fig 1 It is composed of a 12 mm long Michel s agraffe to which a thin metal wire is soldered Insulation of the metal wire was found to be unneccessary The agraffe is securely fastened to the pre senting part of the fœtus using a forceps specially designed for the purpose The agraffe fœtal electrode and forceps are depicted in Fig 2 The second type of fœtal electrode, the suction disc electrode is shown in Fig 3, it is composed of a small plastic disc provided with a hole, either in the bottom or one side

A metal plate to which a thin, 60 cm long metal wire is sol dered is fitted centrally in the bottom of the disc The wire runs in a latex tube and at the end of the latter it is wound around one end of a 3–4 cm long metal tube The latex tube is pulled like a stocking over the joint thus covering and fixing the wind ing rather than soldering the wire to the metal tube is preferred as it facilitates cleaning Another latex tube in connection with a suction apparatus, is attached over the other end of the metal tube Fig 4 illustrates the suction disc electrode fitted to the suction apparatus (Malmstrom type)

Suction discs of different shapes and sizes have been used in our experiments in order to arrive at a type which fulfils the following requirements minimum volume, atraumatic applica tion and use easy handling and stability, all of the four suction discs depicted in Fig 5 are suitable although no 1 seems to be preferable in cases in which cervical dilatation just permits the passage of two fingers and in cases in which the cervical os is directed towards the sacrum The components of suction disc no 1 are shown in Fig 6

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ELECTROCARDIOGRAPHY OF FŒTUS DURING PARTURITION

BY

DANIEL BENVENISTE RICHARD HAMMEN AND HANS PAHLE

Introduction

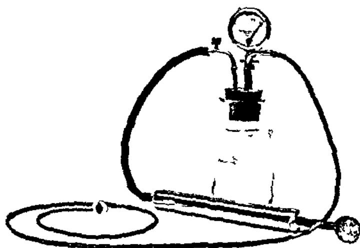
It is important that reliable means are available for assessing the condition of the fœtus during delivery Conventional methods include auscultation of the fœtal heart sounds and inspection of the liquor amnii Usually, these give adequate guidance but they are not ideal

Normal amniotic fluid is clear If intra uterine asphyxia is imminent the amniotic fluid is stained green or brown and is sometimes thick, due to the admixture of meconium However, such changes are sometimes seen in cases in which asphyxia is not imminent and the changes are not always related to the variations in fœtal heart sounds

The most important feature of the heart sounds is the rate, but force and quality may also be important Continuous observation is hardly a practical proposition and there may be considerable variations during the intervals between auscultation Other factors such as obesity, may also make auscultation difficult

In the maternity ward of the Diakonissestiftelse we have endeavoured to overcome these limitations by obtaining electrocardiographic tracings via leads from the presenting part of the fœtus

Fig 3 Suction disc electrode



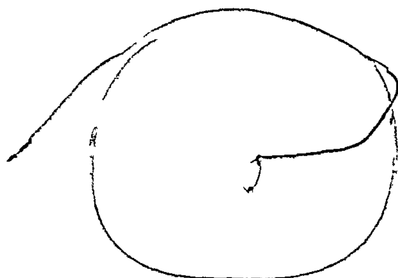


Fig 1 Agraffe electrode



Description of suction disc no 1

This, like the other three discs is made of acryl, it is cylindrical with a diameter of 25 mm and a height of 16 mm The suction disc is provided with a 5 mm side tube of the same material by which it is connected with the latex tube The metal plate of the suction disc is 0 25 mm thick with a diameter of 16 mm it is stabilized centrally in the base of the suction disc by a U shaped metal piece soldered and pressed into the central opening The metal wire is soldered to the arch of the U shaped piece

The suction disc electrode is fastened to the presenting part of the fœtus by negative pressure, maximum 0 1–0 15 atm produced by the suction apparatus

The recorder chosen for the purpose is a twin-channel Mingograph 24 combined with a pre amplifier of the same manufacture (Elema)

The apparatus permits amplification starting at 20 microvolts Paper speed 2 5, 5, 10, 25 50 or 100 mm per second A speed of 25 mm/sec are used routinely whereas speeds of 50 or 100 mm/sec have been used in certain cases in order to have a more satisfactory valuation of the fœtal complexes

Three electrodes lead from the amplifier (1) an active electrode (2) an indifferent electrode, and (3) a neutral electrode

The electrodes are connected to the mother and the fœtus as follows the active electrode is fitted to the metal tube or wire of the fœtal electrode by means of a crocodile clip The indifferent electrode is attached to the lower part of the mother s abdomen either centrally or to one side, using a suction disc such as is commonly used for precordial leads Alternatively a metal plate placed under the maternal buttocks can also be used as the indifferent electrode The neutral electrode is attached to the mother s right leg

The three leads must be sufficiently long to avoid interference with the process of parturition

Fig 7 illustrates diagrammatically the arrangement of the apparatus and the connection of the electrodes with mother and fœtus

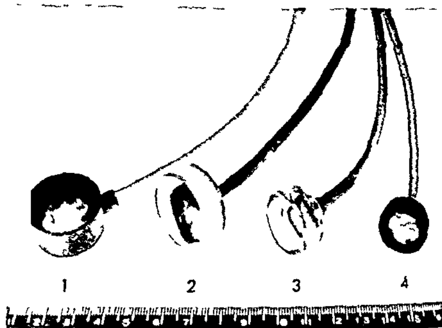


Fig 5 Four types of suction discs

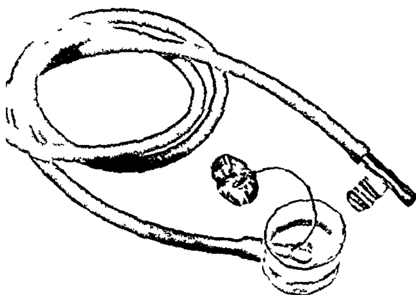


Fig 6 Components of suction disc no 1

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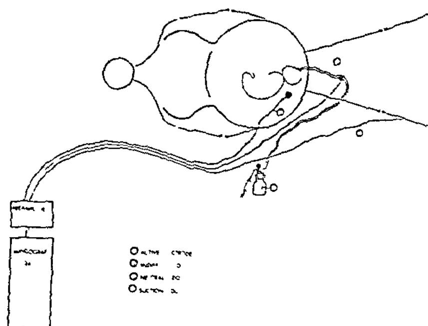


Fig 7 Diagrammatic arrangement of apparatus and application of electrodes to mother and fœtus

Method

The recorder is placed 3–4 metres to the right of the patients bed and is connected to the main electricity supply Earthing must be adequate in order to eliminate interference The suction apparatus is suspended from the edge of the bed, close to the fœtal electrode At this stage vaginal examination is performed. Provided that the cervical dilatation permits the passage of two fingers and that the amniotic fluid has escaped, the selected fœtal electrode is attached to the presenting part of the fœtus Direct vision is not necessary The agraffe electrode is fastened by the forceps designed for the purpose Alternatively, preferably, the suction disc electrode is introduced into the vagina after removal of some of the vaginal discharge, and is fastened to the presenting part of the fœtus adhering to the latter by a negative pressure of 0 1–1 15 atm Care must be taken that the cervical rim is not trapped within the suction disc In other words, this

technique and that for vacuum extraction are identical Finally the three electrodes of the recorder are connected to the mother and the fœtus as described above

Application of the agraffe electrode requires practice and may be rather difficult because it has to be fastened blind If fastened visually the process is easy, rapid, and reliable

Application of the suction disc electrode involves no particular problems

Results

Electrocardiography of the fœtus by the method described was used in 23 cases There were two indications for using the apparatus, either because auscultation had disclosed poor fœtal heart sounds , or because the heart sounds were inaudible, probably on account of the adiposity of the mother

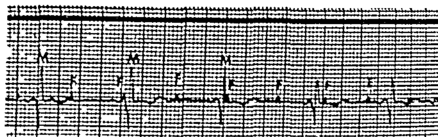
The agraffe electrode was used during labour in 9 cases, the suction disc electrode in 14

The recording periods varied from 30 minutes up to 5 hours with intervals at discretion Records were obtained prior to, during and after labour pains In one case records were obtained also after delivery prior to and after ligation of the umbilical cord

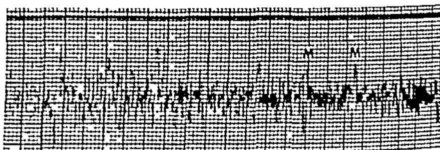
In the 23 cases the frequency ranged between 187–115 beats per minute In 18 cases the frequency dropped during labour pains in the other 5 cases it proved impossible to determine the frequency The drop in frequency was found to be related to the intensity and duration of the contractions, being most marked during severe and protracted pains At the end of contractions the heart returned to normal in all cases except two In one of these cases delivery was completed by vacuum extractor delivery of the other child was natural The latter was very cyanosed at birth but became well after rhinopharyngeal suction combined with oxygen therapy

Application of the two fœtal electrodes did not involve any complications and mothers as well as infants were discharged from hospital in perfect health

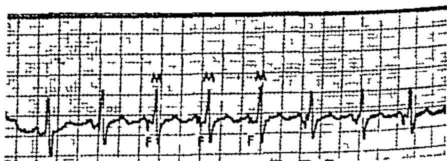
Fig 8 shows two fœtal electrocardiograms obtained by application of the agraffe electrode prior to and during labour pains,



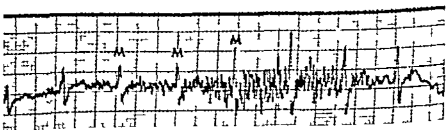
a



b



a



b

Fig 8 Fœtal electrocardiograms obtained by agraffe electrode – a prior to contraction b during contraction

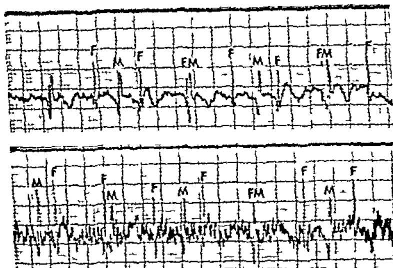


Fig 9 Fœtal electrocardiograms obtained by agraffe electrode

the indifferent electrode being fastened to the left arm of the mother As compared with the maternal complexes the fœtal complexes are small and cannot be distinguished during labour pains

Fig 9 also shows a record obtained by agraffe electrode, the indifferent electrode being fastened in the left iliac fossa of the mother Complexes of mother and fœtus are of equal size and the latter are distinguishable during contractions

Fig 10 shows the same complexes obtained at a paper speed of 50 mm/sec

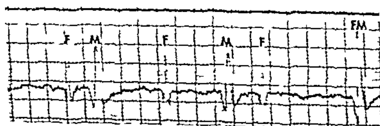
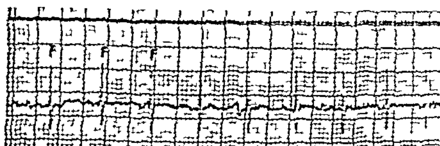


Fig 10 Fœtal electrocardiogram obtained by agraffe electrode at a paper speed of 50 mm/sec



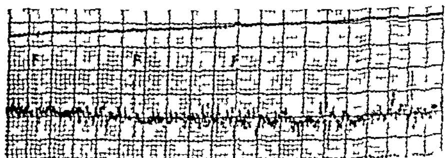
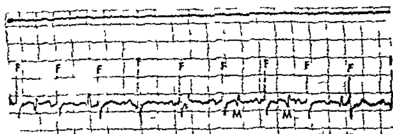


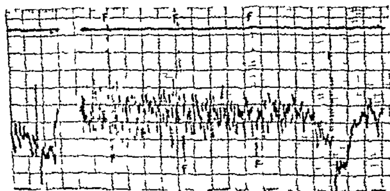
Fig 11 Foetal electrocardiograms obtained by suction disc electrode

Fig 11 shows records obtained by suction disc electrode prior to and during contractions The indifferent electrode is fastened low on the mother s abdomen In this case the picture is different from the previous tracings the foetal complexes are larger than the maternal ones and they are visible during labour pains The foetal frequency prior to contractions is found to be 136 mm/sec to drop considerably during contractions to 68 mm/min Subsequently the frequency remained at a low level in the intervals between contractions and when recording had lasted for 30 minutes delivery by vacuum extractor was decided upon The child was unaffected

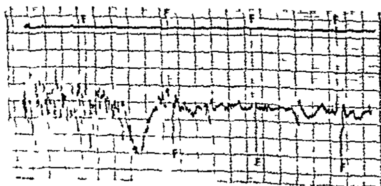
Fig 12 shows foetal complexes obtained by recording for a brief period using the suction disc electrode in this case the cervix was fully dilated The figure includes A complexes during an interval between contractions B during intense contraction, and C after a contraction The drop in frequency is considerable *viz* from 1?5 to 71 remaining at a low level (60



A

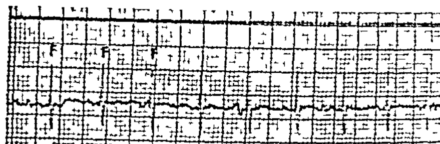


B

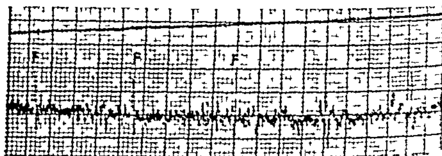


C

Fig 12 Fœtal electrocardiograms obtained by suction disc electrode



A



B

Fig 11 Fœtal electrocardiograms obtained by suction disc electrode

Fig 11 shows records obtained by suction disc electrode prior to and during contractions The indifferent electrode is fastened low on the mother s abdomen In this case the picture is different from the previous tracings the fœtal complexes are larger than the maternal ones and they are visible during labour pains The fœtal frequency prior to contractions is found to be 136 mm/sec , to drop considerably during contractions to 68 mm/min Subsequently the frequency remained at a low level in the intervals between contractions and when recording had lasted for 30 minutes delivery by vacuum extractor was decided upon The child was unaffected

Fig 12 shows fœtal complexes obtained by recording for a brief period using the suction disc electrode, in this case the cervix was fully dilated The figure includes A complexes during an interval between contractions, B during intense contraction, and C after a contraction The drop in frequency is considerable *viz* from 125 to 71, remaining at a low level (60

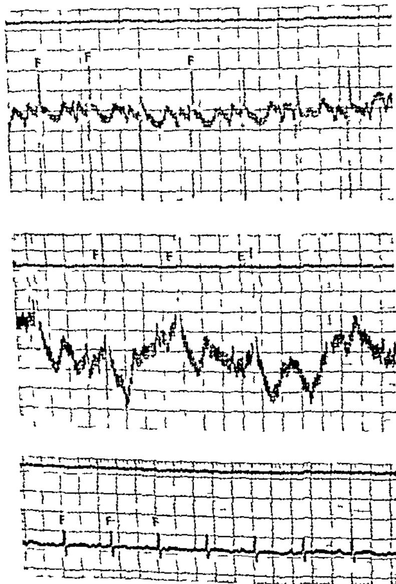


Fig 14 Fœtal electrocardiograms obtained by suction disc electrode

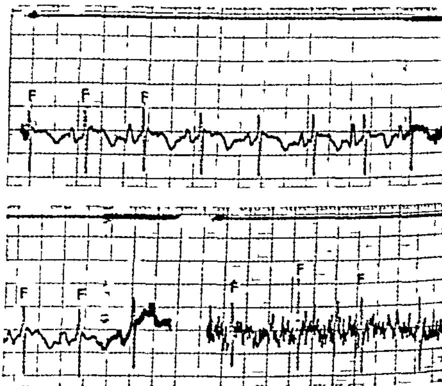


Fig 13 Fœtal electrocardiograms obtained by suction disc electrode

after the contraction) Delivery was natural although the child was very cyanosed, rapid recovery followed suction and oxygen therapy

Fig 13 shows the fœtal electrocardiogram obtained by suction disc electrode in the first of the two cases selected because the heart sounds by auscultation had been found to be poor The fœtal frequency was within normal range (125 per minute), dropping to 100 per minute during contraction, but returning to normal after termination of the contraction (125 per minute) In spite of the findings delivery by vacuum extractor was decided upon The child was unaffected

Fig 14 shows the fœtal electrocardiogram obtained in the other selected case in which heart sounds had been inaudible, probably because of the adiposity of the mother The suction disc electrode was used for the recording The fœtal frequency was found to be within normal range (115 per minute), it dropped during contractions but gradually returned to normal in

the intervals Because of the protracted labour, delivery by vacuum extractor was decided upon The child was unaffected

Fig 15 shows fœtal complexes in a randomly chosen case The suction disc electrode was used for the recording

A) shows complexes in an interval between contractions (136/min), during moderate contractions (150/min), and during intense contractions (71/min), respectively

B) shows complexes during a very intense contraction (68/min), here the indifferent electrode was placed under the buttocks of the mother The complexes are larger, the frequency very low (68/min)

C) shows the complexes immediately after delivery, prior to and after ligation of the umbilical cord The frequency improved from 115/min to 166/min The child was unaffected

Conclusion

Fœtal electrocardiograms with satisfactory fœtal complexes have been obtained even during labour pains Both fœtal electrodes are adequate for the purpose although the suction disc electrode is preferable partly because complexes thus obtained are large and distinct, partly because this electrode is atraumatic and easily attached to the presenting part of the fœtus Which one of the four suction discs is most suitable cannot be decided from the small number of cases so far studied We preferred the one provided with a hole on one side it is particularly well suited for narrow sacrally displaced cervices

The degree of interference on the recording by contractions is related to the intensity of contractions The indifferent electrode has been applied to different sites on the mother s abdomen the groins or iliac fossæ above the umbilicus below the buttocks and above the sacrum to determine at which sites recording conditions are most satisfactory The disturbing interference of contractions was avoided in the case in which the indifferent electrode was placed under the buttocks of the mother

Fœtal complexes are visible as diphasic or monophasic curves It has not yet been possible to valuate the complexes Occasionally their electrical axis changed but the smallness of

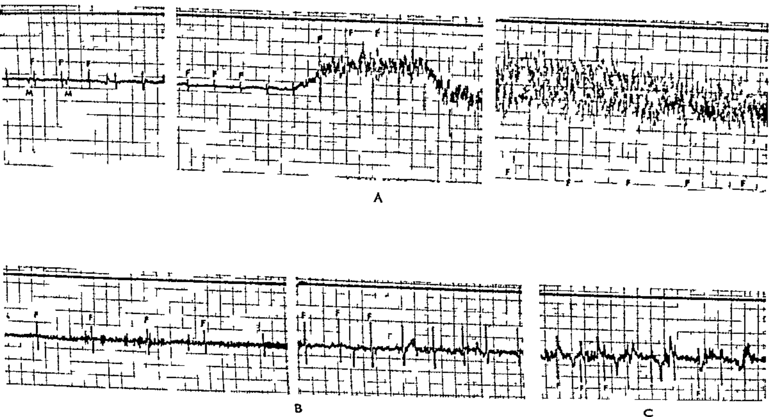


Fig 15 Foetal electrocardiograms obtained by suction disc electrode

clear-cut records of the cardiac frequency which has been ranging between 127 and 115 beats per minute in the cases concerned In 18 cases the frequency dropped during labour pains in 5 cases it proved impossible to determine the frequency during contractions The drop in frequency was found to be dependent on the intensity and duration of contractions, being most marked during severe and protracted pains The fœtal heart action returned to normal in all cases except two, one of these children was very cyanosed at birth, but rapid recovery followed suction and oxygen therapy

The other child was unaffected

The technique involves no complications The method makes continuous recording possible No doubt the method may be elaborated to become applicable as a routine procedure, it may even be combined with an alarm system, thus making remote observation possible

Application of this method is rather limited since cervical dilatation must be sufficient to permit the passage of two fingers and the forewaters must be ruptured

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Received on April 17th 1964

our series does not allow conclusions to be drawn about the applicability of the method for evaluation of anomalies, if any, in the complexes

The method makes continuous recording possible, the patient is not inconvenienced, and the recording does not interfere with the process of delivery The application of the method is limited because the cervical dilatation has to be sufficient of the passage of two fingers and the amniotic fluid must have escaped

Manipulation is uncomplicated and the apparatus is inexpensive Further development would enable continuous recording to be combined with an alarm system thus making remote observation possible The technique would then be more suitable for use as a routine procedure

SUMMARY

In order to have a better knowledge of the condition of the fœtus during labour, we have tried to obtain fœtal electrocardiograms by direct contact with its presenting part through the dilating cervix

In order to obtain such electrocardiograms we have used an electrocardiograph and a fœtal electrode as pick up unit

Is was necessary to design a special fœtal electrode, shaped as a suction disc, which is applied to the foremost part of the fœtus by means of a suction apparatus The pick-up unit is fitted in the bottom of the suction disc and the current led to the recorder, a Mingograph 24 combined with a pre amplifier of the same make ("Elema") The apparatus permits an amplification starting at 20 microvolts

Electrocardiography of the fœtus by the described method was used in 23 cases

The fœtal complexes, which are large and clear, appear as diphasic or monophasic curves It has not been possible to evaluate the complexes fully, in some cases alterations of the electrical axes were noted, but so far it cannot be decided whether the method may serve for the detection of cardiac abnormalities, if any, in the complexes, primarily because the material is too small On the other hand, we have obtained



Abb 1 Der aufgeschnittene Uterus von vorn gesehen

Tötterman L. Erik und Rhen K. Acta obst et gynec scandinav 43 23 1964

Aus der gynäkologisch-obstetrischen Abteilung (L E Tötterman) des Provinzkrankenhauses in Lappland, Finnland

HAMOSTASE DURCH INTRAKAVITÄRE INFUSION VON OCTAPRESSIN®[1]

Ein Fall von Zervikalschwangerschaft

VON

L. ERIK TÖTTERMAN UND KURT RHEN

Die Zervikalschwangerschaft, eine grosse obstetrisch gynäkologische Seltenheit, ist vielleicht doch nicht so ungewöhnlich, wie aus der Literatur hervorgeht 1963 schätzte Turunen die veröffentlichten Fälle auf etwa hundert, eine recht geringe Zahl im Verhältnis dazu, dass der Autor schon 6 publizierte Fälle kannte, in denen die Zervikalschwangerschaft ganz oder nahezu ganz ausgetragen worden war Und doch darf man annehmen, dass auch bei dieser Form der ektopischen Schwangerschaft die allermeisten Fälle bereits im frühen Stadium unterbrochen werden In gleicher Richtung spricht auch eine Statistik aus zwei amerikanischen Krankenhäusern (Paalman und McElin, 1959), nach welcher die Frequenz ca 0,01 % von allen behandelten Schwangerschaften beträgt Demgemäss musste die Zervikalschwangerschaft in ziemlich regelmässigen Abständen in allen obstetrisch gynäkologischen Anstalten vorkommen, in denen mindestens 2000 Entbindungen pro Jahr behandelt werden

Die Prognose der Zervikalschwangerschaft hat sich im Laufe der letzten 20 Jahre weitgehend gewandelt, seitdem man dank der modernen Therapie fast alle Mutter und gelegentlich auch das Kind zu retten vermag Während die Behandlungsresultate quo ad vitam ständig besser geworden sind, ist immer mehr die

[1] Phe²-lys⁸-vasopressin, Sandoz

Frage in den Vordergrund getreten, durch welche operative Massnahme, d. h. mit welchem Resultat quo ad fertilitatem, der Fall zu behandeln ist. In denjenigen Fällen, in denen der Uterus geschont werden konnte, ist das Endresultat nicht selten gut gewesen, und die Patientin hat später geboren (Sherwin und Berg 1960, Thomsen und Johansen 1961).

Der hier vorliegende Fall dürfte trotz der radikalen Operation insofern bedeutsam sein, als er Hinweise für die eventuelle konservative Behandlung gibt.

Beschreibung des Falles

Es handelte sich um eine 39-jährige ledige Gelegenheitsarbeiterin. Keine früheren Schwangerschaften. Die Menstruation 4–5/28 war regelmässig, Ausmass der Blutung und Schmerzen verschieden. Am 20.1.63, zur berechneten Zeit der Menstruation, einen Tag lang Blutung. Danach während einiger Tage Amenorrhoe, wonach fast täglich etwas Blut abging. Am 22.2.63 setzte eine menstruationsartige Blutung ein, die von keinen Schmerzen begleitet war. Als die Patientin am 28.2.63 Kartoffeln aus dem Keller holte, bekam sie Schmerzen im Unterleib, und abends setzte eine starke Blutung ein. Die ganze Nacht hindurch hatte die Patientin aussergewöhnlich schwere Unterleibsschmerzen, die schubweise kamen und gingen. Keine Miktions- oder Stuhlbeschwerden.

Wegen dieser Schmerzen kam die Patientin ins lokale *Krankenhaus*, von wo sie am 2.3.63 zu uns geschickt wurde. Von dort bis in unser Krankenhaus waren es etwa 150 km Autofahrt auf leidlich guter Landstrasse. Die mitgegebene Einweisung enthielt ausser dem schon oben erwähnten *noch* folgendes: Die Patientin hatte viel Blut verloren. Hb morgens 10,4 g/100 cm³, die Senkungsgeschwindigkeit der Blutkörperchen 22 mm. Ferner hiess es in dem Einweisungsschein: Portio ziemlich klein, unmittelbar hinter dem Introitus. Aus dem Os externum uteri ziemlich starke Blutung. Die Zervix *erscheint wie vollgepropft*. Ausserdem noch eine bis zum Nabel reichende Resistenz, die mit dem Uterus in Verbindung zu stehen scheint (*Myom? Corpus uteri?*). Die Anatomie macht einem den Kopf ganz wirr, so etwas habe ich noch nie gesehen. Vor der Abfahrt hatte die Patientin eine Flasche Trockenplasma 500 ml + 1 Amp. Buscopan comp.® bekommen.

Bei der Ankunft um 14.30 Uhr war der Allgemeinzustand leidlich, Blutdruck 140/90. Die Kranke war sehr blass.

Gynäkologische Untersuchung: Muttermund einen Finger weit offen; zu fühlen ist eine feste Masse, die unten nicht an den umgebenden Wänden festsitzt. Ziemlich geringe Blutung. Oberhalb der Symphyse lässt sich eine weiche, faustgrosse Resistenz palpieren.

Wir hielten den Fall zunächst für *missed abortion*, kombiniert mit

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Wir hielten den Fall zunachst fur *„missed abortion"* kombiniert mit

einem Tumor unbekannter Art. Wir vermuteten, der Abort sei im Gange und dass der Muttermund sich während der Autofahrt etwas geöffnet habe. Es wurde beschlossen, den Uterus später zu evakuieren. Es wurden 0,6 ccm Scopomorphin® intramuskulär verabreicht, sowie ½ l Blut als langsame Dauerinfusion. Die Gerinnungszeit und Beständigkeit des Koagulums des aus der Cubitalvene entnommenen Blutes wurden bestimmt, beide waren normal. Um 15.45 Uhr wurde in leichter intravenöser Narkose versucht, den Uterus mit den Fingern und der Abortzange auszuräumen, von dem verabreichten Blut war zu dem Zeitpunkt noch nicht die Hälfte eingetropft. Der Muttermund war noch immer nicht ganz zwei Finger offen. Die herausgeholten Gewebe sahen altem Placentagewebe ähnlich. Die Blutung nahm sofort stark zu, sodass an eine lokale Fibrinolyse gedacht wurde. Nun wurde eine Dauerinfusion von isotonischer NaCl-Lösung, die ε-Amino-Capronsäure enthielt, in dem anderen Arm gegeben, und dem Blut wurden 15 Einheiten Syntocinon® zugesetzt. Die digitale Ausräumung wurde fortgesetzt. Trotz der Verabfolgung von Syntocinon® waren keine Kontraktionen der „Uterushöhle" wahrzunehmen. Dahingegen stellten wir fest, dass sich auf dem Boden der Gebärmutterhöhle eine kleine Öffnung mit festen Rändern befand und dass der bisher faustgrosse, weiche Tumor auf ein Minimum zusammengeschrumpft war, sowie, dass die erwähnte Öffnung offenbar zu dem Tumor führte. Aufgrund dessen wurde die Diagnose Zervikalgravidität gestellt. Die Blutung war die ganze Zeit ziemlich schwer, die Blutinfusion war fast ganz eingetropft, und geeignetes Blut (B) konnte um diese Zeit, am Samstagnachmittag, nicht gleich beschafft werden. Wir machten deswegen den Versuch, mit Hilfe von Octapressin® eine lokale Hämostase herbeizuführen. Einem halben Liter isotonischer Natriumchloridlösung wurden 3 cm³ Octapressin® zugesetzt, der Tropfschlauch wurde in den Boden der Zervikalhöhle geführt, wonach wir die Flüssigkeit frei einfliessen liessen. Nach kurzer Zeit wurde die herausrinnende Kochsalzlösung heller und war bald fast farblos. In der so erzielten Atempause wurden 700 cm³ passendes Blut beschafft, mehr war nicht aufzutreiben. Als die Natriumchlorid-Octapressin®-Lösung aufgebracht war, gaben wir eine zweite Flasche und überlegten, ob man es wagen sollte, den Fall konservativ zu behandeln. Wegen des geringen Blutvorrats entschieden wir uns dann aber doch für die Operation. Für die Zeit des Transports vom Erdgeschoss ins dritte Stockwerk, wo der Operationssaal liegt, wurde die Octapressin®-Infusion fortgenommen, während die intravenöse Syntocinon®-Infusion belassen wurde. Im Operationssaal stellte sich heraus, dass der Blutdruck gesunken war und die Blutung bald wieder eingesetzt hatte. Es wurden Blut und Macrodex® unter Überdrück verabreicht, wodurch der Blutdruck erhöht werden konnte. Danach Operation: Exstirpatio uteri. Inversio appendicis (Totterman). Tiefer Querschnitt. In der Bauchhöhle kein Blut. Uterus sauber, von etwa normaler Grösse. Unmittelbar unten am Corpus setzt das blaurote Collum an, das breiter ist als der Fundus uteri. Die Exstirpation geht leicht vonstatten, weil die Gewebe sich unschwer ablösen lassen. Danach werden die üblichen Ligaturen an

gelegt die Vagina wird exakt geschlossen Peritonisation Die intakte Appendix enthält einen erbsengrossen Fäkalstein sie wird abgetrennt und mühelos invertiert Die Bauchdecken werden wie üblich mit Catgut verschlossen Hautnaht mit Seide Die Patientin überstand die Operation gut Die Heilung verlief abgesehen von etwas längerdauernder subfebriler Temperatur ein wandfrei

Hb am Tag nach der Operation 8 2 g/100 cm³ Am zehnten Tag nach der Operation wurde eine Urographie gemacht weil wir eine Ureterstase befürchteten denn neben dem überdehnten langen und hyperämischen Collum waren besonders breite Gewebsstränge ligiert worden Links wurde eine schlechte Leerung festgestellt Die eine Woche später wiederholte Untersuchung ergab eine schon fast normale Situation

Präparat (C v Numers) Die Wände des Corpus und die Schleimhaut verdickt Mikroskopisch sieht man infolge von Schwangerschaft hypertrophisches Muskelgewebe mit Ödem und kleinen Hämorrhagien Das Endometrium ist dick und weist eine starke deciduale Reaktion sowie eine spärliche Entzündungszelleninfiltration auf Keine Anzeichen von Nidation und auch keine Reste des Eis In der Zervix befindet sich eine Masse die an missed abortion erinnert und hinten links fest adhärent ist Sie reicht nicht ins Bereich des Corpus hinein Mikroskopisch zeigt die eine Probe relativ niedriges keratinisiertes Plattenepithel in der anderen wieder fehlt die Schleimhaut gänzlich In diesen Proben wurden weder Reste des Eis noch Spuren der Nidation gefunden. Die anderen Proben wiesen eine an die Muskelschicht angrenzende und von dicker Thrombose bedeckte Ulzeration auf das Nidationsgebiet wo im Blut und im Muskelgewebe viele choriale Zellen zu sehen waren Eine in die Tiefe gehende Invasion war nicht festzustellen

Diskussion

Unser Fall entspricht gut den Forderungen die an eine Zervikalgravidität gestellt werden (Thomsen und Johansen 1961)

Es wäre in unserem Falle leicht möglich gewesen dass die richtige Diagnose nicht gestellt worden wäre Wenn die Patientin unter der Diagnose „missed abortion" konservativ behandelt worden wäre wäre das Ei vielleicht abgestorben die *Zervix* hyperämie wäre zurückgegangen und eine gewöhnliche, wenn schon vielleicht blutige Abrasio wäre möglich geworden Hätte man andererseits wieder sofort gewaltsam den Uterus ausgeräumt dazu noch ohne ausreichende Vorbedingungen für die Beherrschung des voraussichtlich grossen Blutverlustes, wäre die



Abb 2 Nidationsgebiet mit chorialen Zellen im Muskelgewebe (× 40)

Patientin moglicherweise gestorben Beide Alternativen hätten sehr leicht zu einer irrtumlichen Diagnose fuhren konnen, zunachts zu „missed abortion Wir glauben, dass die zahlenmassige Diskrepanz zwischen den veroffentlichten ausgetragenen Fallen und der Zervikalschwangerschaft uberhaupt z T eben durch die nicht erkannten Falle erklarlich ist

Die Resistenz oberhalb der Symphyse, die anfanglich faust gross und weich, spater klein und fest erschien, war offenbar das Corpus uteri, es war zuerst schlaff, vielleicht mit Koageln angefullt, und kontrahierte sich spater unter der Einwirkung von Syntocinon® Sowohl der makroskopische wie der mikroskpi-

sche Befund des Corpus sprechen dafür, dass die hormonale Funktion des Eis noch – oder wenigstens noch bis ganz kurz bevor – intakt war Leider sind wir nicht auf den Gedanken gekommen, nach der Operation eine Schwangerschaftsreaktion auszuführen

Erst kurzlich hatten wir Octapressin® bekommen und es war in dieser Notlage ein glücklicher Einfall Octapressin®-Losung zur intrakavitären Spulung zu benutzen Nach den Angaben von Sandoz soll dieses Mittel, lokal angewendet, eine kraftige lokale Gefasskontraktion bewirken, während es, in grösseren Mengen intravenos gegeben, eine Vasokonstriktion, besonders des Splanchnikusgebiets, hervorruft Freilich kann das Absinken des Blutdrucks auf 80 mm, das auf dem Weg zum Operationssaal stattgefunden hatte ausser durch die Anstrengung wahrend des Transports auch dadurch bedingt gewesen sein dass die intrazervikale Infusion von Octapressin® abgebrochen wurde womit zugleich die Wirkung der in den Kreislauf gelangten Pressorstoffe aufhorte

Es besteht u E kein Zweifel daruber dass *in diesem Falle die* Blutung durch die Wirkung von Octapressin® gehemmt wurde Die Verabreichung der Infusion und die jähe Abnahme der Blutung fanden gleichzeitig statt, und auf die Unterbrechung der Infusion hin setzte im Laufe von 15 min die Blutung erneut ein

Paalman und McElin (1959) haben die Diagnostik der Zervikalschwangerschaft besprochen Neben den von ihnen genannten Symptomen durfte in manchen fruhen Fallen die Hysterographie gute Hinweise geben Die Zahl der *im fruhen* Stadium diagnostizierten Falle durfte in Zukunft umso mehr zunehmen als die fruhe Mutterschaftsfursorge immer besser wird und die Kenntnis von der Moglichkeit und den Symptomen der Zervikalgravidität sich bei den Arzten verbreitet

In den fruhzeitig diagnostizierten in situ Fallen kann therapeutisch ausser den Prinzipien und Massnahmen die Thomsen und Johansen (1961) aufgrund eigener und von anderen Autoren stammender Erfahrungen dargelegt haben auch noch die primäre Abtotung des Eies durch intraovulare Injektion von z B durch 20 %ige Natriumchloridlosung (Bengtson *et al* 1962), in Frage kommen Auf diese Weise durfte man in kurzer



Abb. 2. *Nidationsgebiet mit chorialen Zellen im Muskelgewebe* (× 40)

Patientin möglicherweise gestorben. Beide Alternativen hätten sehr leicht zu einer irrtümlichen Diagnose führen können, zu nächst zu „missed abortion". Wir glauben, dass die zahlenmässige Diskrepanz zwischen den veröffentlichten ausgetragenen Fällen und der Zervikalschwangerschaft überhaupt z. T. eben durch die nicht erkannten Fälle erklärlich ist.

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Zeit die auf hormonalem Boden zustandegekommene Hyperämie der Zervix zum Ruckgang bringen konnen Eine rasche Austreibung des abgestorbenen Eies, wie bei der Corpusschwangerschaft, ist bei der Zervikalgravidität wohl kaum zu erwarten, und die so in der Zwischenzeit erfolgte Abnahme der Hyperamie kann dann fur die endgultige Behandlung des Falles sehr bedeutsam sein

Wir haben in einigen Fallen Octapressin® als intrauterine Infusion angewandt, wenn die postpartale Blutung nicht zufriedenstellend sistierte, obwohl eine Abrasio vorgenommen worden war, der Uterus sich in guter Kontraktion befand und am Muttermund keine blutenden Gefässe aufzufinden waren Das Resultat war gut Wir haben auch versucht, bei wegen Placenta prævia ausgefuhrten Schnittentbindungen hartnäckige Blutungen im Bereich des unteren Segments mit Octapressin®-Losung zum Stehen zu bringen, aber ohne Erfolg Vielleicht hängt dieser Misserfolg damit zusammen, dass die Losung unter diesen Umstanden nicht ins Lumen der Gefasse oder in die umgebenden Gewebe einzudringen vermag Wir haben auch daran gedacht, diese Behandlungsmethode bei schwer blutenden, schlecht kontraktilen Abortfallen anzuwenden, haben aber bisher noch keinen passenden gehabt Ferner haben wir einmal einer Patientin mit blutenden Œsophagusvarizen Octapressin® Losung zu trinken gegeben Die Blutung sistierte daraufhin, aber spater begannen die Varizen erneut zu bluten, und die Behandlung blieb dann erfolglos (Seppalä, 1963) Bei der genannten Behandlung sind keine Komplikationen von seiten des Herzens oder des Blutdrucks vorgekommen

Das Material ist sehr klein, und die Resultate erlauben somit keine sehr weitgehenden Schlussfolgerungen Wir wollten aber trotzdem auch diese kleine Serie uber den Gebrauch von Octapressin® veroffentlichen, weil innerhalb der nachsten Zeit voraussichtlich kein zweiter Fall von Zervikalgraviditat zu uns in Behandlung kommt Der oben beschriebene ist bisher der einzige in unserem Krankenhaus diagnostizierte Fall von Zervikalgravidität unter ca 15000 behandelten Schwangerschaften Auch geeignete Falle von missed abortion und Geburtsblutungen kommen nicht oft vor

ZUSAMMENFASSUNG

Es wird ein Fall von Zervikalschwangerschaft beschrieben, bei welchem durch Infusion von Octapressin® Lösung in die Zervikalhöhle Hämostase herbeigeführt wurde. Es werden einige Gesichtspunkte zu der Frequenz, Diagnose und Behandlung der Zervikalgravidität dargelegt. Ferner werden gewisse Möglichkeiten für die intrakavitäre Anwendung von Octapressin® erörtert.

SUMMARY

One case of cervical pregnancy is reported where hæmostasis was established by injecting Octapressin® solution in the cervical cavity. Some aspects regarding frequency, diagnosis and treatment of cervical pregnancy are given. Certain possibilities of using Octapressin® intracavitary are discussed.

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Am 20. Mai 1964 erhalten.

Liliequist B and Lindgren L. Acta obst et gynec. scandinav 43 240 1964
From the Department of Diagnostic Radiology (Bengt Liliequist, M D) and the Department of Obstetrics and Gynæcology (Professor Per Lundstrom) University of Umea, Sweden

HYPERFLEXION OF THE UTERUS AND INFERTILITY

BY

B LILIEQUIST AND L LINDGREN

Hyperflexion of the uterus is a common finding in patients with primary infertility, according to descriptions found in current gynæcological text-books (Huffman, 1962, Parsons and Sommers, 1962, Willson, Beecham and Carrington, 1963) The uterus is also frequenly hypoplastic (Novak and Novak, 1956, Martius, 1960) and cervical stenosis is considered to be a consequence of the hypoplasia (Seitz and Amreich, 1955) *Primary infertility is therefore often treated* by instrumental dilatation of the cervix (Javert, 1959, and others)

Asplund in 1952 showed that the isthmus of the uterus is narrowed during the secretory phase and Jonsson-Lindgren *in 1964 found that the shape of the uterus changes during* the menstrual cycle In order to study the significance of the hyperflexion of the uterus in infertile women and to demonstrate a possible variation of the degree of flexion of the uterus *during the menstrual cycle we have reviewed the hystero*salpingograms of infertile women examined at the hospital of Umea during the years 1960 to 1963

Method

The hysterosalpingographies were performed according to the technique devised by Kjellberg in 1942 In most cases we used *the instrument constructed by* Malmstrom *in* 1961 The X-ray examinations were performed with the uniform technique As contrast medium 35 % Perjodal viskos H® was used

The patient was examined in the supine as well as in the prone position The angle between the prolongation of the longitudinal axis of the cervix and the longitudinal axis of the corpus was determined on lateral views At a stretched position of the uterus the degree of the angle has been denoted as zero The degree of anteflexion is stated as a positive angle and the degree of retroflexion as a negative angle In four cases the hysterosalpingography was performed in the supine as well as in the prone position, with a horizontal beam direction The angles were estimated as −15° and −14°, +104° and +93° −121° and −124° and −28° and −27° respectively, the figure found in the supine position given first

The width of the isthmus was measured on lateral views as well as on frontal views In some cases the width of the isthmus could not be determined as the corpus of the uterus was projected on top of the isthmus This appearance was commonly seen in hyperflexion of the uterus

The statistical analysis was performed by using Students t test

Material

The entire series comprises 370 hysterosalpingographies performed at the hospital of Umea during the years 1960 to 1963 Examinations sh wing changes in the shape of the uterus due to pathological conditions such as fibromyomas or other tumours and examinations which were technically unsatisfactory were ex cluded The remaining material consists of 225 hysterosalpingo graphies

The material was grouped according to parity The examina tions in nulliparous women were further divided into three groups

Group 1 Women who consulted for primary infertility and where no explanation for the infertility could be found in subsequent investigations

Group 2 a Women who attended because of primary infertil ty and where tubal occlusion, oligospermia (≤ 20 million sperms per ml) or menstrual cycles of an anovulatory character were found

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of ovulation was determined by measurements of the basal temperature and in some cases also by endometrial biopsy

A further classification was made according to the degree of flexion of the uterus measured on the X ray films Examinations in which the angle was +90° or more were classified as hyperanteflexion of the uterus, angles from −90° and below were classified as hyperretroflexion of the uterus Angles between +90° and −90° were classified in a third group called flexion of the uterus (Fig 1) The two groups with hyperflexion of the uterus (> +90° and < −90°) were collected in one group termed hyperflexion of the uterus The group classified as flexion of the uterus, was further divided into one group with angles from zero to +90°, called anteflexion of the uterus and another with angles from zero to −90°, termed retroflexion of the uterus

Results

Flexion of Uterus in the Different Groups

The distribution of the degree of flexion of the uterus among the different groups (1–5) is seen in Figures 2, 3 and 4 Table I shows the distribution according to age among groups 1–4 The greatest frequency of hyperflexion of the uterus is found in group 1, i e among women who attended because of primary infertility and where it was not possible to find any explanation for the infertility at subsequent examination In this group hyperflexion of the uterus is twice as common as in group 2, i e among women who came either for reasons other than primary infertility or for primary infertility which could be explained by tubal occlusion, oligospermia or anovulatory men-

Table 1 *Distribution of age in groups 1–4*

Group	Hyperflexion	Flexion
1	30 4 ± 0 5	29 0 ± 0 6
2a	33 8 ± 1 3	31 1 ± 1 3
2b	24 8 ± 2 7	30 5 ± 2 7
3	29 3 ± 1 7	32 3 ± 0 8
4	38 6 ± 2 5	37 1 ± 0 8

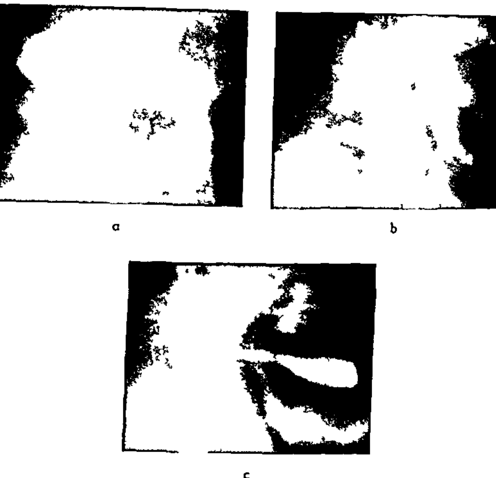


Fig 1 Hysterosalpingographies Lateral views
a) hyper anteflexion *b*) flexion *c*) hyper retroflexion

Group 2 b Women who attended for other reasons (dysmenorrhœa and menstrual irregularition)

Examinations of parous women were also divided into three groups

Group 3 Women who attended because of secondary infertility

Group 4 Women who attended for other reasons

Group 5 Women examined by hysterosalpingography after the menopause

The cases were also grouped according to the time of ovulation in relation to the time of examination The occurrence

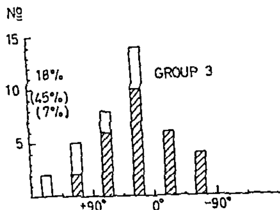


Fig 3 Flexion of the uterus in parous women
Group 3 Women who attended because of secondary infertility (unhatched areas show women with previous abortion who have not borne children)

strual cycles The difference is 33 2 ± 11 5 per cent (0 01 > P > 0 001)

In comparing groups 3 and 4 i e women who have been pregnant and who consulted for secondary infertility and women who consulted for reasons other than secondary infertility, the same tendency is evident (0 05 > P > 0 01) This difference can be explained by the fact that 45 5 per cent of women who pre viously had suffered abortion but not borne children showed hyperflexion of the uterus In contrast to this, women in the same group who had borne children showed hyperflexion of the uterus in only 7 per cent (0 05 > P > 0 01) On the other hand there was no difference in the degree of flexion of the uterus in the rest of group 3 compared with group 4

Width of isthmus

The average width of the isthmus has been correlated with the time of examination in the menstrual cycle (Fig 5) In con formity with Asplund (1952) we found that the isthmus is narrowed when the examination was performed in the secretory

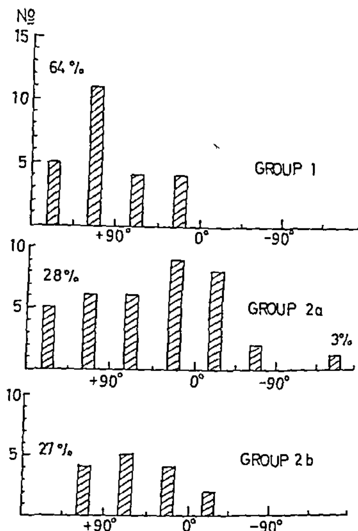


Fig 2 Flexion of the uterus in nulliparous women

Group 1 Women who consulted for primary infertility without any explanation to the infertility being found at subsequent investigation

Group 2 a Women who attended because of primary infertility and where tubal occlusion oligospermia (≤ 20 million sperms per ml) or menstrual) cycles of an anovulatory character was discovered

Group 2 b Women who attended for other reasons (dysmenorrhœa and menstrual irregularities)

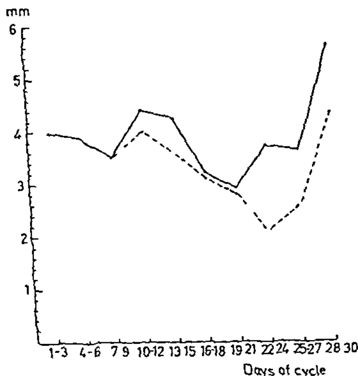


Fig 5 Average width of the isthmus in mm correlated with the time of examination in the menstrual cycle

flexion of the uterus The difference amounts to 0 50 ± 0 14 mm (P < 0 001) In comparing groups 2 and 1, the sagittal width of the isthmus is on the average 0 86 ± 0 14 mm (P < 0 001) wider in group 2 than in group 1 This difference is valid even if the different width of the isthmus at different times during the menstrual cycle is taken into consideration and also in the case ovulation has occurred A corresponding difference is also obtained if the width of the isthmus is *measured on frontal views* (Table III)

Within the group 3 and 4 *i e* parous women the conditions are rather reversed, in women with hyperflexion of the uterus

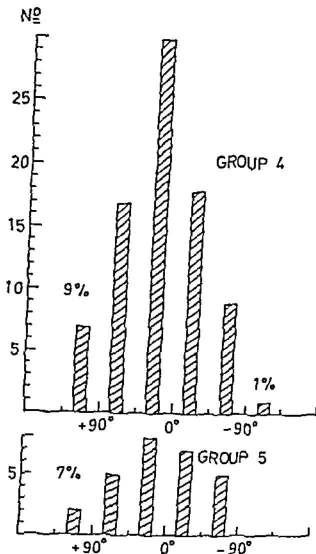


Fig 4 Flexion of the uterus in parous women
Group 4 Women who attended *for reasons other than secondary infertility*
Group 5 Women examined after the menopause

phase and especially when ovulation has occurred In Table II the average width of the isthmus in the sagittal plane within the different groups has been correlated with the appearance of hyperflexion or flexion of the uterus during the proliferatory and secretory phases respectively Within groups 1 and 2, *i e* nulliparous women the isthmus is wider when there is hyper-

the isthmus has a tendency to be narrower However, the series is too small to permit any reliable conclusion (P = 0 10)

In group 4, the sagittal width of the isthmus is on the average 0 41 ± 0 18 mm wider than in group 3, in conformity with the difference found between group 1 and 2 (0 05 > P > 0 01)

In hyperflexion of the uterus there was no acute angulation either at the isthmus or at the cervix Usually, the shape of the cavity had the appearance of an even bow (Fig 1)

Flexion of the uterus correlated with the time during the menstrual cycle

In Fig 6 the examinations have been grouped in regard to hyperflexion anteflexion and retroflexion of the uterus In the group with anteflexion of the uterus the degree of flexion is less in examinations performed when ovulation had occurred than in examinations performed without any signs of ovulation Accordingly, the uterus seems to have a tendency to straighten up after ovulation It is evident from the shape of the curve in Fig 6, that there is a similar tendency to a stretching of the uterus pre and postmenstrually Similar conditions are also found in the group with retroflexion of the uterus and also if the examinations are grouped according to parity The flexion of the uterus was less in examinations performed during the secretory phase after the occurrence of ovulation than in examinations performed during the proliferative phase or when ovulation did not occur This stretching of the uterus after ovulation is statistically significant for the whole material (P = 0 001) which is also evident from Table IV In the group with hyperflexion of the uterus there is, however a tendency in a reverse direction as the hyperflexion of the uterus apparently seems to increase following ovulation The difference is, how ever not statistically significant (Table IV)

Discussion

The observation described previously, that hyperflexion of the uterus can be a cause for primary infertility has been confirmed by this investigation A high incidence of hyperflexion

Table II *Average width of the isthmus in the sagittal plane in mm during the proliferative and secretory phases*
P = no signs of ovulation S = signs of ovulation

Group	Hyperflexion 4—12	N	Hyperflexion 13—27 P	N	Hyperflexion 13—27 S	N	Flexion 4—12	N	Flexion 13—27 P	N	Flexion 13—27 S	N
1	3 3±0 4	6	2 5±0 2	4	2 1±0 2	6	2 7±0 5	3	1 5±0 2	3	3 0	2
2	4 0±0 5	3	4 0±0 6	8	3 3±1 1	4	3 2±0 4	10	3 1±0 3	13	2 7±0 4	12
3	3 7±0 3	3	—	0	2 0	1	3 8±0 9	12	3 2±0 5	10	2 4±0 2	10
4	2 6±0 4	5	2 5	2	4 0	1	4 1±0 3	33	4 3±0 5	16	3 1±0 2	22
Total	3 3±0 2	17	3 4±0 4	14	2 8±0 4	12	4 1±0 3	58	3 7±0 3	42	2 8±0 1	46

Table III *Average width of the isthmus in the frontal plane in mm during the proliferative and secretory phases*
P = no signs of ovulation S = signs of ovulation

Group	Hyperflexion 4—12	N	Hyperflexion 13—27 P	N	Hyperflexion 13—27 S	N	Flexion 4—12	N	Flexion 13—27 P	N	Flexion 13—27 S	N
1	5 8±0 5	4	4 0	2	4 0	2	4 0±0 5	3	3 5	2	3 5	2
2	5 0	2	5 9±0 9	8	4 5±1 1	4	5 9±0 4	10	5 0±0 4	10	4 1±0 5	11
3	9 0	1	—	0	—	0	6 4±0 9	10	6 8±0 8	9	4 8±0 6	10
4	5 3±0 3	3	—	0	—	0	6 5±0 4	29	5 9±0 5	15	6 6±0 3	21
Total	5 8±0 1	10	5 5±0 8	10	4 3±0 8	6	6 2±0 3	52	5 7±0 3	36	5 4±0 4	44

the isthmus has a tendency to be narrower However, the series is too small to permit any reliable conclusion ($P = 0.10$)

In group 4, the sagittal width of the isthmus is on the average 0.41 ± 0.18 mm wider than in group 3, in conformity with the difference found between group 1 and 2 ($0.05 > P > 0.01$)

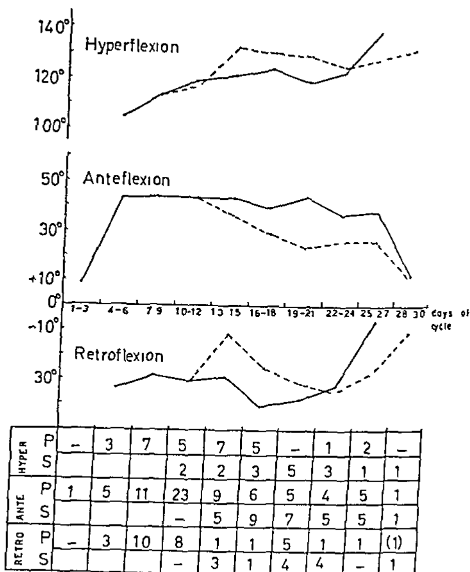
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Flexion of the uterus correlated with the time during the menstrual cycle

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Discussion

The observation described previously that hyperflexion of the uterus can be a cause for primary infertility has been confirmed by this investigation A high incidence of hyperflexion



HYPER	P	–	3	7	5	7	5	–	1	2	–
	S				2	2	3	5	3	1	1
ANTE	P	1	5	11	23	9	6	5	4	5	1
	S				–	5	9	7	5	5	1
RETRO	P	–	3	10	8	1	1	5	1	1	(1)
	S				–	3	1	4	4	–	1

Fig 6 The degree of flexion of the uterus during the proliferative and *secretory phases The cases have been grouped according to hyperflexion,* anteflexion and retroflexion Below, the number of cases in the different groups is shown

of the uterus is also found in women who have suffered abortion but not borne children and who consulted because of secondary infertility The frequency of hyperflexion of the uterus in parous women who attended because of secondary infertility was the same as in the control group

Table IV The average degree of hyperflexion and flexion of the uterus during proliferative and secretory phases
P = no signs of ovulation   S — signs of ovulation

Group	Hyperflexion 4—12	N	Hyperflexion 13—27 P	N	Hyperflexion 13—27 S	N	Flexion 4—12	N	Flexion 13—27 P	N	Flexion 13—27 S	N
1	115±7	6	1 9±8	4	127±11	6	54±11	3	53°	2	39±10°	3
2	126±13	3	123±8	8	133±4	4	26±7	10	40±6	13	35±8°	11
3	106±7	3	141	1	131±5	3	44±7	12	42±7	9	26±7	10
4	110±5	5	108	2	127	1	39±5	36	37±5°	14	25±4	19
Total	115±4	17	124±6	15	129±3	14	39±3	61	40±3	38	28±3	43

In this series the isthmus in non pregnant women was wider in the group with hyperflexion of the uterus than in the group *with flexion of the uterus* This was valid when the width of the isthmus was measured on frontal as well as on lateral views Accordingly, *hyperflexion of the uterus does not seem to cause* any narrowing of the isthmus However, the isthmus was less wide in women who consulted because of *primary* infertility without any explanation for the infertility being found than in women where an explanation was found or hysterosalpingography was performed for indications other than primary infertility These conditions are in all probability due to the fact that hypoplasia of the uterus may be a cause of primary sterility In previously pregnant women a corresponding increase in the width of the isthmus could not be established This group does not include enough cases with hyperflexion of the uterus to allow for any reliable conclusions An acute angulation of the isthmus or cervix caused by hyperflexion of the uterus could not be found in any case in this series

The investigation also shows that when there is no hyperflexion of the uterus, the degree of flexion is less during the secretory phase if ovulation has occurred than when signs of *ovulation lacks There is thus a stretching of the uterus during* the secretory phase when the uterus is under the influence of progesterone During the same period the isthmus is narrowest (Asplund, 1952) and the cavity of the uterus has its largest volume (Jonsson-Lindgren, 1964) These changes are believed to be caused by the influence of the motility of the uterus during the menstrual cycle Moreover, there is a tendency to straightening of the uterus during the pre- and postmenstrual periods In the group with hyperflexion of the uterus, there is no corresponding stretching of the uterus during the secretory phase, but rather an increase in the hyperflexion of the uterus when ovulation has occurred

Sources of error include variations in the projection of the angle between the corpus and cervix with version and lateroflexion of the uterus, variations in pressure applied for introduction of the contrast medium, as well as individual variations in the flexion of the uterus These are all of significance when the

results of the examination are estimated The variations obtained are large and show the same trends when the cases are classified in different groups and with ante and retroflexion of the uterus They are statistically significant It is therefore considered safe to conclude that there is stretching of the uterus when ovulation has occurred As there is a connection between hyperflexion of the uterus and primary infertility and no narrowing of the width of the isthmus can be shown to occur, the increase of the hyperflexion of the uterus by the influence of the motility of the uterus probably is a contributory cause to primary infertility A closer explanation for this mechanism cannot be given however, as our present knowledge of the motility of the uterus is incomplete

Conclusion

Flexion of the uterus has been assessed by hysterosalpingography in 62 women examined because of primary infertility and 39 women examined because of secondary infertility The findings are compared with those in 15 nulliparous women, 82 parous women and 27 women after the menopause The investigation corroborates the observation that hyperflexion of the uterus is common in women with primary infertility In nulliparæ the isthmus is wider when there is hyperflexion of the uterus than when there is no hyperflexion In women, who consulted because of primary infertility without an explanation for this being found, the isthmus is constantly narrower in hyperflexion as well as in flexion of the uterus than in women where an explanation for the infertility was found and in nulliparæ examined by hystersalpingography for indications other than primary infertility The investigation also shows that the uterus has a tendency to stretch after ovulation except when there is a hyperflexion of the uterus

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A CASE OF GONADAL DYSGENESIS WITH PHALLIC ENLARGEMENT AND A 45/XO KARYOTYPE

BY

K BOCZKOWSKI J PHILIP AND J TETER

The first reports of gonadal dysgenesis described special forms of this syndrome which were characterized by various degrees of phallic enlargement together with the presence of interstitial Leydig like cells in the dysgenetic gonad, del Castillo *et al* (1947) Russell and Swyer (1952), Gordan *et al* (1955) The histological description of such dysgenetic gonads is found in publications of Grumbach *et al* (1955) and in the textbook of Jones and Scott (1958)

Fourteen cases of Turner s syndrome studied in the Department of Endocrinology during the years 1958–1960 included three cases with phallic enlargement

With the development of cytogenetic methods the problem arose whether the male determining Y chromosome is present in such cases This problem has not yet been elucidated De la Chapelle (1962), among 23 cases of Turner s syndrome which he studied cytogenetically found only one case with phallic enlargement In this case the karyotype was 45/XO Lindsten (1963) in his monography on cytogenetic and clinical examinations of 57 cases of Turner s syndrome did not report any case with phallic enlargement

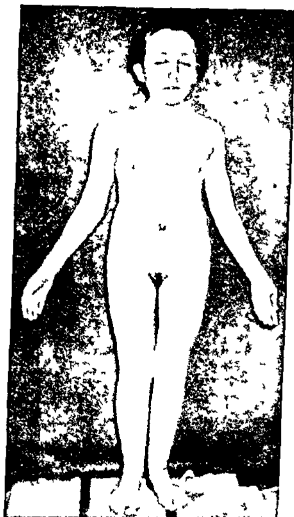


Fig 1 Case B J aged 19 years — Turner s syndrome

Case Report

Patient B J aged 19 years, was referred with the diagnosis of "Turner s syndrome with virilization , complaining of menopausal symptoms No spontaneous menstruation had occurred Height 133 cm arm span 140 cm weight 35 kg The chest was barrel shaped (Fig 1) The neck was short and slightly webbed There was a cleft palate The spine was markedly curved Seborrhoea and slight temporal baldness were present The breasts were completely infantile without any signs of pubertal changes The pubic hair was scanty The clitoris was hypertrophied (Fig 2) Labia minora were only developed in the upper 1/3 and very thin The vagina was narrow and elongated with smooth, inelastic walls



F g 2 Photograph of exterr al gen tal a of pat ent B J Note canty pubic hair and an enlarged cl tor s

Urinary excretion of p tuitary gonadotrophins was 112 m u/24 hrs and 266 m u /24 hrs on two d fferent examinations 17 ketostero ds 8 3 mg/24 hrs (upper normal range) Vaginal smears showed no œstrogen c activity

Laparotomy showed an underdeveloped uterus with long and thin Fallopian tubes In the pos tions usually occupied by the ovaries thin white "streak" gonads 3 4 cm long and 0 5 cm thick were present B lateral gonadectomy was performed

H stological exam nation d sclosed that both gonads conta ned a cortical zone resembl ng ovarian connective stroma The medullary zone showed degenerative changes In th s zone s ngle elongated cells were found resembl ng to a certa n degree Leyd g cells In the deeper layers were numerous small tubules of mesonephrot c origin There were no primord al foll cles

Cytolog cal exam nation Examination of smears from the buccal mucosa showed negat ve sex-chromatin pattern

Leucocytes from peripheral blood were cultured according to the method of Moorhead et al (1960) with slight modifications Forty technically well spread metaphase plates were counted (Table I) Five cells with 45 chromosomes were analyzed with the aid of enlarged microphotographs All of them showed the

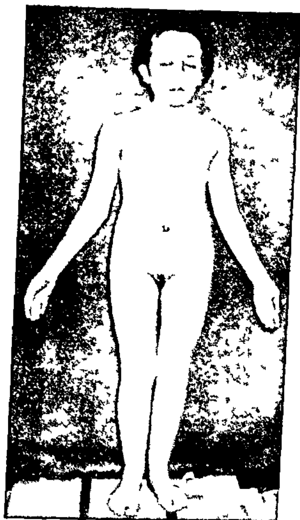


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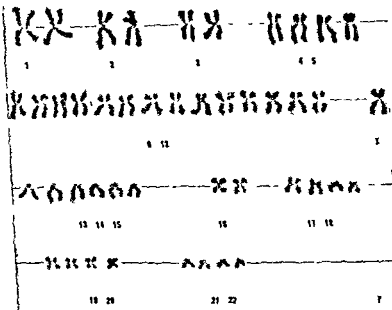


Fig 4 Karyotype of cell shown in fig 3

Furthermore histological examination of the dysgenetic gonad showed absence of fully developed Leydig cells The medullary zone of the dysgenetic gonad presented some degenerative characteristics Therefore the morphological basis for the hyper trophy of the clitoris is uncertain We will analyze this problem in the light of recent findings

To simplify the problem it is accepted that in the somatosexual development the process of determination and differentiation of the male sexual organs is as follows the male chromosome pattern—46/XY determines the formation of the testis which normally produces fœtal androgenic substances The testes dif ferentiate the internal and external genitalia in the male direc tion with a simultaneous inhibition of female structures originat ing from the Mullerian ducts

The question arises what is the origin of the masculinization

Table 1 *Karyotype Analysis*

No of Chromosomes	43 or Less	44	45	46	47	Total
Cells counted	2	9	28	1	–	40
No of cells analyzed	–	4	5	–	–	9

karyotype 45/XO, (Fig 3, 4) Four cells with 44 chromosomes were also analyzed and showed no constant pattern We concluded that these were artificial changes, which probably arose during the making of the preparations possibly by heating It was therefore assumed, that the modal number was 45 with the sex chromosome constitution XO

Discussion

This case of Turner's syndrome with phallic enlargement is evidence for the concept that virilization of the external genitalia does not necessarily indicate the presence of a Y-chromosome

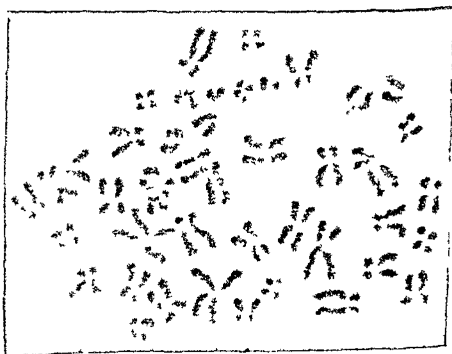


Fig 3 Metaphase from cultured blood

SUMMARY

This rare case of Turner s syndrome with phallic enlargement shows that masculinization of the external genitalia is not associated either with the presence of a Y-chromosome or with the presence of properly developed Leydig cells in the medullary zone of the dysgenetic gonad In this case, as in other cases of Turner s syndrome with negative chromatin pattern the karyotype was 45/XO

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of the external genitalia of a patient with the karyotype 45/XO Usually in such patients the dysgenetic gonad contains clumps of Leydig-cells which can develop without the presence of a Y-chromosome, Polani (1963), Grumbach (1963) What is then the true ætiology of the hypertrophy of the clitoris in Turner's syndrome with the karyotype 45/XO and without Leydig cells?

Hypertrophy of the clitoris may be the result of androgenic hyperactivity of the adrenal cortex The 17-ketosteroids in our patient never exceeded 8 3 mg/24 hrs (fractionated determination of 17-ketosteroids unfortunately could not be carried out)

The other possibility is the one suggested by Grumbach (1963) Partial masculinization of the external genitalia may be connected with the androgen hyperactivity of Leydig cells at the fœtal period and/or at puberty There is no absolute correlation between the degree of efficiency of gonadal activity in these two periods During the fœtal period Leydig cells might have been active and then atrophied In the present case the medullary zone of the gonad showed features of degeneration Grumbach, on the other hand, stresses that the interstitial tissue of the dysgenetic gonad may produce small quantities of androgens, even when Leydig cells can not be clearly distinguished in the histological picture He also notes that clumps of Leydig cells may, in such cases, be situated outside the gonad

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Case Reports

Case 1 – (8374/59) The patient aged 38 years, had been married for two weeks Her menstrual periods had been normal and very nearly painless On October 16 1959 on the 12th day of the cycle, she woke up with acute low abdominal pain and was admitted to the hospital two and a half hours later There was nausea and vomiting but no signs of shock The right lower abdomen was tender with muscular rigidity but apart from tenderness on palpation gynecological examination was normal Seventeen hours after the onset of pain the leucocyte count was 19 600 axillary temperature 37 1 C and rectal temperature 37 8 C Preoperatively no diagnosis could be made At operation a moderate amount of chocolate-coloured fluid was present in the abdomen a a result of rupture of a right sided adherent ovarian chocolate cyst the size of an apple In the left ovary there were several small foci of endometriosis and a small intact tarry cyst A right salpingo-oophrectomy with left ovarian resection and appendicectomy was performed Patho-anatomical examination (C von Numers) Bilateral ovarian endometriosis The patient made an uneventful recovery and was discharged on October 27 1959

Case 2 – (5910/61) The patient aged 42 years had been married for 13 years She had had two spontaneous deliveries the last eight years previously Menstruation had been normal and painless During menstruation on the fifth day of the cycle the patient felt sudden intense low abdominal discomfort with nausea and vomiting She was admitted on August 1 1961 two hours after the onset of abdominal pain On admission her general condition was good There was tenderness in the right lower abdomen but no muscular rigidity Axillary temperature was 38 1 C and rectal temperature 38 3 C The patient was observed for three hours She had rigors and the temperature rose to 39 3 C Muscular rigidity was then present over the whole abdomen The leuocyte count was 15 700 The preoperative diagnosis even after gynecological examination was acute appendicitis At operation a moderate amount of chocolate-coloured fluid was found in the abdomen The innocent appendix was removed and operation continued through a lower median incision Intense peritoneal inflammation was found and in the left ovary adherent to the posterior leaf of the broad ligament there was a ruptured tarry cyst the size of a large plum The right ovary was apparently normal Left salpingo-oophorectomy was performed Patho-anatomical examinat on (K Dammert) revealed no signs of endometriosis Macroscopically the diagnosis was certain however The patient was discharged on August 11 1961 recovered.

Case 3 – (821/62) The patient aged 48 years had been married for 15 years She had had one spontaneous delivery 14 years previously Menstruation had been normal and painless The patient was admitted to hospital on January 20 1962 complaining of lower abdominal pain and nausea for one day The pain had started suddenly on the 23rd day of the menstrual

Koskela Osmo Acta obst et gynec scandinav 43 262 1964

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RUPTURE OF OVARIAN ENDOMETRIAL CYSTS

BY

OSMO KOSKELA

Endometriosis occurs in the ovaries as superficial, dark brown patches or as chocolate or tarry cysts of varying sizes Endometrial cysts may rupture when the intracystic pressure becomes sufficiently great Occasionally, when the cyst ruptures into the abdominal cavity, the discharge of old blood causes sudden severe abdominal pain In such a case surgical intervention may be indicated, as shown for example by Novak (1931), the Finnish gynæcologist Ingman (1950), and, on the basis of a *larger series, by* Pratt, Higgins *and* Foust *(1952)* The latter found only fifteen reported cases of ruptured endometrial cysts causing acute abdominal symptoms up to 1945, and added 10 cases of their own

The first to report rupture of an endometrial cyst as a complication of pregnancy was Scott, in 1944 This complication has since been described by Nelson and Fandrich (1950), Pratt *et al* (1952), Brill *et al* (1957), Noel (1961), and Steinberg (1962) These were all reports of single cases Because reports on ruptured endometrial cysts requiring surgical intervention are so infrequently published it seems desirable to detail the following five cases, one of them occurring in association with an intrauterine pregnancy These cases were operated on in the Gynæcological and Obstetrical Department of the Central Hospital of Southern Saimaa during the period April 1955 to March 1964

Tarry material escaped through the perforation into the abdomen A left oophorectomy and right ovarian resection was performed. Patho-anatomical examination (K. Dammert) Bilateral ovarian endometriosis The patient was discharged on June 6 1693 fully recovered

Discussion

Rupture of a large endometrial cyst causes sudden abdominal pain nausea and vomiting The temperature is often elevated There is elevation of the leucocyte count, abdominal tenderness and muscular rigidity Often there are pronounced symptoms of pelvic peritoneal irritation immediately after the onset of abdominal pain The patient s general condition, however, is good and no signs of shock are present

The diagnosis is often difficult to make preoperatively The relative infrequency of this condition and the consequent general unfamiliarity with it seem to be responsible for the fact that the correct diagnosis is rarely achieved before operation The illness is usually diagnosed as acute appendicitis ruptured ectopic pregnancy ovarian hæmorrhage or twisted ovarian cyst However, the sudden severe abdominal pain, the muscular rigidity and increase in temperature appearing within a few hours of the onset of pain do not fit into the picture of appendicitis The above symptoms as well as the good general condition and the absence of signs of shock are not common in cases of massive ovarian hæmorrhage and ruptured ectopic pregnancy The symptoms associated with small ovarian hæmorrhages which are fairly common have been reported to be considerably milder than those due to ruptured ovarian endometrial cysts (Koskela) If a twisted ovarian cyst causes symptoms of this degree the cyst is generally palpable at gynæcological examination During the last trimester of pregnancy rupture of an endometrial cyst is often diagnosed incorrectly as concealed accidental hæmorrhage (Brill *et al* Noël) Treatment is conservative surgical operation

In two of the present writer s cases rupture of an endometrial cyst occurred during a regular menstrual period but in two the rupture was unrelated to menstruation Finally one case ruptured

cycle The axillary temperature was 38 2° C and rectal temperature 38 9° C There was tenderness and muscular rigidity in the lower abdomen. The leucocyte count increased from 9 600 to 13 900 The diagnosis could not be established preoperatively At operation tarry material was found in the abdomen The peritoneum was inflamed In the left ovary there was a ruptured adherent tarry cyst and on the right a smaller cyst, which was intact. Due to the age of the patient subtotal hysterectomy with bilateral salpingo-oophorectomy and appendicectomy was performed Patho-anatomical examination (C von Numers) Bilateral ovarian endometriosis The patient was discharged on the tenth postoperative day fully recovered.

Case 4 – (7629/62) The patient, aged 24 years had been married for three months She had always been healthy Menstruation had been normal and painless The last mentrual period had begun 6 1/2 weeks previously She was admitted on September 2, 1962, because she had had sudden, severe low abdominal pain, nausea and vomiting for one day Her general condition was good The axillary temperature was 36 8° C and rectal temperature 38 2° C The leucocyte count increased from 8 400 to 16,700 There was tenderness and muscular rigidity over the entire abdomen. The pregnancy test was positive Preoperatively the patient was thought to have a twisted ovarian cyst complicating pregnancy At operation dark brown tarry fluid was found in the abdominal cavity The peritoneum showed intense inflammation and was reddened The uterus was enlarged and its size about that seen in the 2nd month of pregnancy In the left ovary there was an adherent ruptured cyst larger than a woman s fist, and tarry material escaped from it into the abdominal cavity The right ovary was larger than usual and adherent posteriorly and to the right of the gravid uterus Left salpingo-oophorectomy was performed. Patho-anatomical examination (C von Numers) Ovarian endometriosis The patient made an uneventful recovery and was discharged on the tenth postoperative day She was delivered at the calculated time of a viable foetus which presented by the breech At the time of writing the patient is in the sixth month of her second pregnancy and she has had no untoward symptoms

Case 5 – (4939/63) The patient aged 32 years and married was admitted on May 27 1963 eight hours after the onset of abdominal pain She had woken up in the early morning with acute abdominal discomfort and nausea during menstruation The axillary temperature was 37 8° C and rectal temperature 38 2° C Examination showed tenderness and muscular rigidity in the lower abdomen The leucocyte count was 10 800 No gynecological examination was made before operation While the patient was being observed tenderness and muscular rigidity over the abdomen increased The preoperative diagnosis was acute appendicitis At operation chocolate-coloured fluid was found in the abdominal cavity and the innocent appendix was removed The operation was continued through a subumbilical midline incision a ruptured adherent cyst, about the size of a man s fist was found in the left ovary and a typical focus of endometriosis was present in the right ovary

Tarry material escaped through the perforation into the abdomen A left oophorectomy and right ovarian resection was performed. Patho-anatomical examination (K. Dammert) Bilateral ovarian endometriosis The patient was discharged on June 6 1693 fully recovered

Discussion

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In two of the present writer s cases rupture of an endometrial cyst occurred during a regular menstrual period but in two the rupture was unrelated to menstruation Finally one case ruptured

spontaneously in the first trimester of pregnancy In regard to the time of occurrence of the rupture, this series supports the opinion advanced by Meyer (1930), which Kahanpää endorses (1946), *viz* *that ruptures of endometrial cysts can occur at any* time during the menstrual cycle Meyer and Kahanpää have related this observation to the general discussion on the ætiology of external endometriosis No doubt this observation might give support to Sampson's ætiological theory, if it were only possible to prove the existence of ruptured endometrial cysts presenting only slight symptoms or no symptoms at all However, the existence of such ruptures continues to be entirely hypothetical even though several investigators seem to have accepted this possibility and even consider it common (Novak, E, 1931, *Scott*, 1944, Kahanpää, 1946, Ingman, 1950, Pratt *et al*, 1952, TeLinde, 1961, Novak and Woodruff, 1962) The rupture is thought usually to produce slight symptoms because chocolate cysts are so adherent to the neighbouring structures and the amount of tarry material escaping from the cyst is small (Scott, Kahanpää, Ingman, Pratt *et al*, TeLinde, Novak and Woodruff)

As in the cases described above, the clinically verified cases *of ruptured endometrial cyst cause such intense abdominal* symptoms that the frequent occurrence of rupture with only slight symptoms may be questioned Indeed according to Albrecht (1955) such ruptures do not occur Heim s (1959) opinion, an even more radical one, is expressed in his supplement on endometrois We are convinced that chocolate cysts only rupture as the result of major traumatic influences, *e g* operative intervention *The spontaneous rupture so frequently claimed* to exist seems to us to be a call for the development of certain theories rather than a clinical fact This opinion appears very categorical Perhaps it might be said with more reason that the denial of the existence of spontaneous ruptures seems to us to be a call for the development of certain theories rather than a clinical fact

Reports on rupture of endometrial cysts during pregnancy are extremely rare In five cases previously described the rupture occurred during the last trimester of pregnancy (Scott, Nelson and Fandrich, Brill *et al*, Noel, Steinberg) and in only

one case in the first trimester (Pratt *et al*), as it did in Case 4 of the present series During pregnancy the enlarging uterus uterine contractions and the descent of the foetal head may all cause rupture of the cyst (Scott, *Brill et al*, Steinberg)

SUMMARY

Five cases of ruptured endometrial cyst operated on because of acute abdominal symptoms are reported One of the patients was six and a half weeks pregnant at the time the endometrial cyst ruptured The typical symptoms produced by rupture of an ovarian endometrial cyst are acute abdominal pain, nausea and vomiting muscular rigidity developing in a few hours, distinct elevation in leucocyte count and in temperature In spite of definite signs of peritonitis the general condition is good It seems that endometrial cysts can rupture spontaneously at any time during the menstrual cycle

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DYSGERMINOMA OF THE OVARY

A clinical report of 20 cases

BY

O KOLLER AND H GJONNÆSS

Dysgerminoma of the ovary has recently attracted considerable clinical interest The prevalence of the tumour among girls and young women where the preservation of the childbearing function is highly desirable, may make the choice between radical and non radical therapeutic procedures a very crucial one At the same time there are widely divergent opinions as to the adequate treatment

An anlysis of 102 cases, all reported since 1949, by Pedowitz, Felmus and Grayzel (1955) revealed that following unilateral salpingo-oophorectomy 17 of 47 cases of encapsulated dysgerminoma developed tumour in the remaining ovary within a relatively short period The authors recommend bilateral salpingo oophorectomy and total hysterectomy followed by deep X ray therapy regardless of encapsulation of the growth and age of the patient Thoeny, Dockerty, Hunt and Childs (1961) arrived at the same conclusion based on 27 cases from the Mayo Clinic Fourteen of the patients underwent unilateral salpingo oophorectomy None of these patients exhibited clinical signs of dissemination at the time of laparotomy, but recurrence occurred in 6 of them

On the other hand Swedish authors (Sjovall, 1943, Santesson, 1947, Kottmeier, 1960, Brody 1961) report favourable results after conservative surgery followed by low to moderate

doses of radiation to the pelvis on the affected side and the lumbar region, but sparing the remaining ovary Brody (1961) describes 17 cases, of these 4 had adhesions, one had ruptured tumours and 2 had metastases The five year survival rate was 94 per cent and the recurrence rate 25 per cent Eighteen pregnancies occurred in 10 patients after treatment Of the 16 babies one had congenital malformations

In spite of these reasonably favourable results, this scheme of treatment has been questioned by all the participants in a recent discussion of the problem (Pedowitz Huffmann, Moss and Editor of the Am J Obst & Gynec 1963), mainly because of the high rate of recurrence, the risk of malformed babies in the first generation and the number of mutations passed on to subsequent generations Moss argues that the radiotherapist does more harm than good if he treats too small a volume of tissue or administers an insufficient dose because the chances of cure during the initial stages may be lost If postoperative radiation is chosen, he recommends treatment of the whole pelvis, lower abdomen and paraaortic area delivering a midabdomen dose of at least 2000 r The editor comments that if one elects on the basis of clinical judgment to perform a unilateral oophorectomy, one should stand on this decision and should not employ unilateral pelvic radiation Pedowitz and Huffmann advise that before any decision is made a conference should be held with the patient and her family The possible lines of treatment should be openly discussed the calculated risk inherent in preserving the child bearing function should be stressed and balanced against the psychological results of sterilization

Brody (1961) points to the wide variation in five year survival rate given by different authors from 27 1 per cent (Pedowitz *et al* 1955) to 75 per cent in his own series from the Radiumhemmet He suggests that this disparity may be mainly due to three factors selection of the patients the treatment adopted and the extent of follow up examinations One important factor is the histologic criteria adopted for the diagnosis

As pointed out by Santesson (1947) and Santesson and Marrubini (1957) there is considerable difference between the prognosis of pure dysgerminomas and prognosis of tumours where

dysgerminoma like tissue is mixed with other structures of the germ-cell type, the latter being far more malignant. Brody's series comprises only pure dysgerminomas while both the series of Pedowitz *et al.* (1955) and of Thoeny *et al.* (1961) include mixed tumours, 3 of 102 and 2 of 27 cases respectively. These small numbers do not seem to change the results to any significant degree. But, as stressed by Pedowitz *et al.*, a more thorough histological examination of the specimens might have revealed more of these mixed types. The data definitely indicate that the results of treatment in pure and mixed types of dysgerminoma should be listed separately. As a basis for this differentiation a complete and detailed histological examination is necessary.

The series to be presented here is a retrospective survey dating back to 1932. Four cases already published by Ahnfelt (1951) are included. In view of the rarity of the tumour and the many unsolved problems involved in its clinical management, it is felt that all available data should be published.

Material

The material comprises 20 cases including all cases treated at the Norwegian Radium Hospital in the period 1932 to 1962, which have been histologically classified as dysgerminoma or dysgerminoma like. The pathological anatomical laboratory had the whole surgical specimen for examination in 10 cases. In the remaining 10 cases blocks were provided from other pathological laboratories according to the rules of The Norwegian Radium Hospital to ensure uniform histologic evaluation. In 2 of the cases a metastasis removed from the left supraclavicular region was the sole material available for the histological diagnosis, in the remaining cases the primary tumours were examined. Seventeen of the cases were classified as pure and 3 as mixed dysgerminomas. All 3 mixed tumours had, in addition to dysgerminoma like tissue, large areas suggestive of embryonal carcinoma with adenomatous and papillomatous structures. In 1 of the cases some trophoblast-like cells were seen. The primary operations were in all but one case performed in other hospitals.

In the period 1932–1962, 1378 cases with malignant ovarian

Table I

Age Groups – Years	Observation Time – Years <1	1–5	>5	Total
9–14	2 (2)[1]	1	1	4 (2)
15–19	0	2	0	2
20–24	1 (1)	2	1	4 (1)
25–29	0	0	3	3
30–34	0	1	1	2
35–39	0	1	1	2
40–49	2 (2)[2]	0	0	2 (2)
Over 49	0	0	1 (1)[3]	1 (1)
Total	5 (5)	7	8 (1)	20 (6)

Number of patients who died in parenthesis
[1] Both mixed tumours
[2] One mixed tumour
[3] Dead 10 years after treatment Recurrence suspected but not proved

tumours were referred for treatment to The Norwegian Radium Hospital giving an incidence of dysgerminoma or dysgerminoma like tumours of 1 45 per cent (20/1378)

As the hospital is an institution primarily for radiation therapy, this figure cannot be considered as indicative of the true incidence

Clinical data

The ages of the patients and observation of survival times are given in Table I The cases of mixed tumours are indicated

All the patients were normally developed except for one, who had consulted a doctor because of primary amenorrhœa In this case the operation revealed aplasia of the right ovary

Including this last case 6 of the patients were premenarchal Only one patient had passed the menopause and she was 70 years of age

The initial symptoms were abdominal pain in 10 patients 4 of whom were admitted to the hospital as emergencies with the diagnosis of acute abdomen 7 patients had noticed a tumour or swelling of the abdomen one a tumour of the left supraclavicular region and one had no local subjective symptoms, but gradually increasing general weakness

Six patients had had symptoms of less than one month and 15 of less than 6 months duration Of the remaining 5 patients all had a history of more than one year s duration

The tumour was macroscopically diagnosed as unilateral and localized with intact capsule in 11 cases Rupture of the capsule only was found in 3 cases (one of them a mixed tumour), lymph node metastasis in 5 cases (2 of them mixed tumours) and gross bilateral tumours in one case

Bilateral salpingo-oophorectomy was performed in 5 cases of pure dysgerminoma in spite of the normal appearance of the other ovary *In one of these the histologic examination* revealed tumour tissue in both ovaries Serial sections were not performed and therefore one in 5 must be taken as a minimum frequency for involvement of the contralateral macroscopically normal ovary

Recurrences in the conserved ovary after conservative operation without additional radiation may also indicate the frequency of unsuspected bilateral involvement This happened in 2 of the 4 cases of pure dysgerminoma so treated

Adding these 2 groups together gives a figure of 3 out of 9 cases with unsuspected bilateral involvement

Radiation technique Until 1952 X-ray treatment was performed with a 175 kV machine, 4 Ma, filter 1 mm Cu, focal skin distance 50 cm Daily dose 300 r, (skin dose) From 1952 a 200 kV machine was used with 15 Ma, otherwise unchanged technical data Since 1959 the X-ray beam of a 31 MeV betatron has been used with a daily tumour dose 200 r (measured with a Victoreen ionization chamber in water)

Unilateral salpingo-oophorectomy was the primary operation in 12 cases

Included are all 3 cases with mixed tumours

A 27 year old woman (316/59) had extensive involvement of the lymph nodes both in the pelvis and in the paraaortic area The unilateral salpingo-oophorectomy was evidently an incomplete operation Postoperative radiation with combined X ray and betatron amounting to about 3600 r tumour dose had practically no effect and the patient died less than 6 months after the primary operation

A 9 year-old girl (719/58) with rupture of the capsule at the primary operation had a second laparotomy 6 weeks afterwards The operation revealed

a rapid progression of the disease with peritoneal implants in the pelvis and enlarged firm lymph nodes retroperitoneally along the aorta The remaining cystic ovary was removed but contained no tumour tissue X ray therapy to pelvis and lower abdomen with tumour dose about 3500 r was given but the patient died 10 months after the primary operation with local recurrence

A 11 year-old girl (605/59) with a left sided primary tumour adherent to the posterior abdominal wall and the sigmoid colon had postoperative X ray treatment to the pelvis and lower abdomen with a tumour dose of about 1540 r Local recurrence developed however, in the right side of the pelvis within 1 month of completion of the treatment. Additional X ray therapy was given with a total tumour dose of about 3300 r but the tumour continued to grow, and the patient died less than 7 months after the first operation.

In 4 of the patients with well localized and pure dysgerminomas no postoperative radiation was given in order to preserve reproductive function

A 27 year-old woman (1717/52) in whom the size of the primary tumour was not stated developed enlargement of the remaining ovary about 4 months after the primary operation. Because a recurrence could not be excluded a laparotomy was performed and the cystic ovarian tumour removed Histological examination revealed simple cysts but no signs of dysgerminoma This patient has remained well for 11 years without additional radiation therapy

The other 3 patients developed recurrences within 3 years

An 11 year-old girl (660/62) with a grapefruit-sized primary tumour of the left ovary had a further operation 9 months afterwards because of a tumour in the remaining ovary The operation also disclosed a tumour located on the left uterine cornu and lymph node metastases in both sides of the pelvis and along the aorta On the side of the primary tumour an egg sized lymph node was found in the hilar region of the kidney A tumour dose of 4000 r was given by betatron to the pelvis and 3600 r by X rays (skin dose) to the paraaortic area postoperatively The patient has been quite well for nearly 2 years

A 9-year-old girl (2403/54) with an orange-sized primary tumour developed a grapefruit sized dysgerminoma in the remaining ovary 3 years after the primary treatment The ovary was removed and X-ray therapy was given to the pelvis and the lumbar region 1500 r skin dose to each field The observation time is 9 years since the primary treatment with no signs of recurrence

A 18-year-old girl (18-7/61) had been operated upon at the age of 15 because of a dysgerminoma in the right ovary A further laparotomy 3 years later revealed a retroperitoneal tumour medial to the caecal pole and thus corresponding to the lymph chain cranial to the infundibulo-pelvic ligament. Histological examination proved this tumour to be of dysgerminomatous type

The cystic left ovary was als removed Histological examination revealed endometriosis and a follicle cyst, but no tumour tissue Postoperatively the patient was treated by betatron to the pelvis and paraaortic area with a tumour dose of 3000 r to 3900 r Victoreen

She is quite well more than 2 years afterwards

The remaining 5 patients subjected to unilateral salpingo-oophorectomy all had postoperative irradiation as a part of the primary treatment None of them has shown any signs of recurrence In 3 of these patients the tumour was localized and the capsule intact In one case there was a small, probably metastatic nodule in the infundibulo-pelvic ligament, which was not removed These 4 patients were treated with radium and had additional X-ray therapy to 2 anterior and 2 posterior large fields covering the pelvis and lower abdomen with a skin dose of 2800-3900 r The last patient had a rupture of the capsule She was treated by betatron 4000 r to the pelvis and 3600 r to the lumbar area

Bilateral salpingo-oophorectomy was the initial surgical therapy in 6 cases

A 70-year-old woman (631/41) with a localized tumour and intact capsule had no postoperative irradiation She died in a local hospital 10 years later with abdominal tumours Autopsy was not performed

A 30 year-old woman (5/35) with bilateral ovarian involvement had a very small radiation dose, 400- 200 r skin dose to 2 anterior and 2 posterior large fields The treatment was stopped because of severe nausea The patient has been living without any signs of recurrence for 28 years

A 22 year-old woman (306/49) with an unilateral encapsulated pure dysgerminoma had intrauterine and intravaginal radium application at The Norwegian Radium Hospital She was discharged and advised to have X ray treatment at a local hospital but it has not been possible to confirm that this treatment was carried out The patient died in a local hospital 11 months after institution of the treatment Autopsy was not performed

The 3 remaining patients had all a full course of postoperative radiation by betatron Tumour doses varied between 3600 r and 5000 r Two of them had localized and encapsulated tumours In one case the capsule was ruptured and there were enlarged pelvic lymph nodes which were not removed All 3 patients are living without signs of recurrence 2–4 years after treatment

Radiation therapy was the initial and sole treatment in 2 cases

A 27 year-old woman (1209/47) had as the first symptom noticed a tumour in the left supraclavicular region for one month She was admitted to a local hospital where the tumour was removed and histologically diagnosed as a metastasis from a dysgerminoma The patient was referred to The Norwegian Radium Hospital where the examination revealed an orange-sized nodular and movable tumour on the right side of the uterus and a grapefruit-sized tumour in the left hypochondrial region fixed to the po terior abdominal wall

She was treated with X rays 3500 r skin dose to the left supraclavicular region The same dose was given to both an anterior and a posterior field in the left hypochondrial region and the right side of the pelvis The tumours proved to be very radio-sensitive and rapidly disappeared Five months after completion of the treatment however a tumour had developed in the left untreated side of the pelvis and also in the left inguinal region. Both tumours were firm and fixed X ray therapy to the recurrences was given in similar doses as given previously but this time without any definite effect The patient died 10 months after the first admittance to the hospital

A 21 year-old woman (1553/61) had had uncharacteristic abdominal pains for 3 months At an exploratory laparotomy a large and fixed retroperitoneal tumour was found emerging from the pelvic cavity obviously inoperable No biopsy was taken The patient was referred to The Norwegian Radium Hospital where also a group of enlarged lymph nodes in the left supraclavicular region was found Biopsy showed metastasis from dysgerminoma During the subsequent 3 weeks hydrothorax developed on the left side The patient was treated with X ray 3600 r skin dose towards the left supraclavicular region and betatron in 3 continuous fields including mediastinum lumbar region and the pelvis 3000 r tumour dose The tumour responded rapidly but an enlarged adnexal tumour remained Another laparotomy revealed this to be an enlarged ovary There were no other signs of recurrence The ovary was removed The histologic examination showed fibrotic changes and no signs of residual tumour This patient is quite well 2 1/2 years later

Discussion

One major limiting factor for a conservative operation is the incidence of clinically undetectable spread to or development in the contralateral ovary The present admittedly small, series supports the figures of Pedowitz *et al* (1955), indicating this incidence to be about 1/3 In addition to bilateral extension is the risk of other types of spread especially lymph node metastasis Three of the four patients with pure dysgerminoma in the present series where conservative surgery without additional radiation were given a trial had recurrences Brodys series (1961) with postoperative low dose irradiation also had a recurrence rate of

The cystic left ovary was als removed Histological examination revealed endometriosis and a follicle cyst, but no tumour tissue Postoperatively the patient was treated by betatron to the pelvis and paraaortic area with a tumour dose of 3000 r to 3900 r Victoreen

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Radiation therapy was the initial and sole treatment in 2 cases

cervix with its mucous secretion may be important to a young woman With œstrogen substitution therapy, and there seems no reasons to deny her this, she may be able to live a normal sexual life except for the reproductive capacity

Previous reports as well as the present study clearly demonstrate the high radiosensitivity of the pure dysgerminoma Surprisingly small doses may *in some* cases be *sufficient for* permanent cure On the other hand Brody (1961) admits that small tumour doses are sometimes inadequate In our cases we have used large tumour doses from 3000 to 4000 r In this connection it may be appropriate to refer to the male counterpart of dysgerminoma, the seminoma Not only the histological, but also the clinical characteristics of these two types of tumours are very similar Seminoma also is highly radiosensitive The results from The Norwegian Radium Hospital, (Høst and Stokke 1959) indicate, however, that the best over all cure rate is achieved by doses of 3500 to 4000 r These authors add that preferably high voltage treatment should be employed because of the favourable distribution of the dose

Of the 3 mixed tumours in the series all died within the first year in spite of irradiation therapy with tumour doses from 3300 r to 3600 r The data support previous reports that mixed tumours, as compared with pure dysgerminomas are highly malignant and relatively radio-resistant (Santesson and Marrubini 1957)

The homologous tumours in the testis have similar clinical characteristics, which may indicate that therapeutic principles applied in the treatment of these tumours may also be valid for mixed ovarian tumours According to Dixon and Moore (1953) mixed testicular tumours with a seminomatous component should probably be treated by resection of testes, cord and retroperitoneal lymph nodes Høst and Stokke (1958) suggest that high irradiation doses (4000 to 5000 r) be given a trial —With the poor prognosis of the mixed dysgerminomatous ovarian tumours in mind these lines of treatment should probably be considered

SUMMARY

A report is given on 17 pure dysgerminomas and 3 tumours containing dysgerminomatous tissue mixed with structure of embryonal carcinoma type

25 per cent An important clinical point is, however, that in spite of the high rate of recurrence, the 5-year survival rate in Brody's material was as high as 94 per cent In the present series all recurrences were apparently cured by radiotherapy This high cure rate of the recurrences undoubtedly is due to the high radiosensitivity of the tumour

The tumour may, however, spread rapidly after a conservative operation, as exemplified by one of the reported cases in this series, where wide dissemination had occurred 9 months after primary operation In spite of the high radiocurability of the pure dysgerminomas, it is difficult to escape the conclusion that such spread in some cases may ruin the chance for permanent cure

The risk of recurrences caused by hidden bilaterality (spread or bilateral development) may perhaps be decreased by earlier diagnosis, but this seems otherwise to be an absolute obstacle to successful conservative operation

Theoretically, regional lymphadenectomy might be effective in preventing spread on the affected side without compromising the fertility Removal of lymphatic tissue along the common iliac, external iliac and hypogastric vessels is a relatively simple procedure This also holds for resection of the lower half of the ovarian vessels It is interesting to note that the lower part of the ovarian vessels probably was the only site of recurrence in one of our conservatively treated patients Clearing of the paraaortic area and the hilar regions of the kidneys may be a too extensive surgical procedure in patients with pure dysgerminomas This area, however, may be irradiated without undue risk for the preserved ovary, especially when using a well delineated X-ray beam as from a betatron

If it is decided to make no attempt to preserve fertility, bilateral salpingo-oophorectomy with total hysterectomy followed by a complete course of radiation has been recommended as a so called radical therapy

It seems questionable if total hysterectomy has any rational basis as a routine part of the treatment of pure dysgerminoma if there is no direct infiltration of, or implantation on the uterine surface Neither the uterine cavity nor the cervix have been proved to be potential areas for metastasis Preservation of the

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SARCOMA OF THE UTERUS

BY

ERIK HØRLYCK AND CLAUS PETRI

Introduction

This study was designed to review the clinical and pathological features of uterine sarcoma, with a particular view to defining the group endometrial sarcoma

Considering the rarity of this disease and its sparse mention in Scandinavian literature, the diagnostic and therapeutic problems, created by 2 cases of endometrial sarcoma seen within a short period prompted us to review this heterogeneous group of tumours

Classification

In previous publications including a few Danish reports (Juhl, 1945 Okkels and Terkelsen 1933, Kryger, 1948), these tumours have been classified on a purely cytomorphological histological basis, using the designations round spindle , polymorpho , giant cell types without paying regard to the site or ætiology of the tumour

In recent literature there is broad agreement on the following classification

(1) endometrial sarcoma	(a) pure sarcoma
	(b) carcinosarcoma
	(c) mixed mesodermal sarcoma
(2) myometrial sarcoma (leiomyosarcoma)	(a) primary
	(b) secondary

Observation time for the *pure dysgerminomas* was from 2 to 28 years, in 8 cases more than 5 years

Histologically proven bilaterality occurred in 2 of 6 cases where both ovaries were removed at the primary operation In only one of the 2 cases was tumour tissue macroscopically recognizable

Among 4 patients with apparently localized tumours treated primarily solely by unilateral salpingo-oophorectomy 3 patients developed recurrences during a period from 9 months to 3 years In 2 of the patients the contralateral ovary was involved The third recurrence might perhaps have been prevented by resection of the lower half of the ovarian vessels with their accompanying lymphatic tissue All 3 recurrences were apparently cured after operation and full irradiation

Two patients with pure dysgerminomas died because of proved recurrences, both within the first year

The effect of radiation therapy was striking, even in patients with wide spread dissemination

The 3 patients with *mixed tumours* died all within the first year in spite of irradiation therapy with tumour doses from 3300 to 3600 r Experiences from treatment of the homologous testicular tumours indicate that surgery should include lymphadenectomy and that the radiation dose should be higher

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Aetiology

Nothing definite is known about the aetiology of uterine sarcomas However, the aetiology of carcinosarcoma and mixed mesodermal sarcoma has been the subject of special discussion (Ober and Tovell, 1959, Symmonds, Dockerty and Pratt, 1957) Ober (1959) has reviewed the embryology of these two types of tumour in an excellent paper He concluded that the common origin is the endometrial stromal cell which, although highly differentiated, is the most pluripotent cell derived from the Müllerian mesenchyme This cell is the source of pure sarcoma cells as well as heterologous elements and malignant glandular epithelium The latter is of mesodermal, not ectodermal, origin Thus there is no question of teratoma

The possibilty of X ray irradiation being an aetiological factor in the development of uterine sarcoma remains uncertain Some authors have found a possible causal relationship (Boutselis and Ullery, 1962 Symmonds and Dockerty, 1955, Walsh, 1955) For instance Symmonds and Dockerty (1955), in an analysis of 19 cases of mixed mesodermal tumours, found 4 in patients who – several years previously – had X ray castration because of intractable uterine bleeding In contrast, none of Sternbergs *et al* (1954) 38 patients with uterine sarcoma had received X ray irradiation Among 10 patients with uterine sarcoma in the Surgical Department of the Frederiksborg County Central Hospital Hillerod listed in Table II, one had 10 years previously undergone X ray castration because of menorrhagia (Case 5 Table II)

Pathology

Gross Appearances

A typical finding in a not too advanced case of endometrial sarcoma is a uterine cavity dilated by a polypoid tumour with a pink, shining smooth surface showing varying degrees of haemorrhagic infarction and necrosis The tumour is friable and readily bleeding As a rule it arises in the fundus uteri

Instead of a polypoid tumour there may at times be a diffuse spread of sarcoma in the endometrium

Table I

	Leiomyosarc	Sarc Endom.	Mixed Mesoderm	Carc. Sarc.	Botryoid
Webb	22	5	8	5	4
Boutselis	14	5	12	2	3

(3) sarcoma from other tissue elements in the uterus, i e connective tissue and vessels, e g hæmangiosarcoma, lymphosarcoma, reticulosarcoma, pericytoma

Metastatic tumours are outside the scope of this study

Incidence

Sarcoma of the uterus is not extremely rare According to the literature, sarcomas constitute 1 8–2 6 per cent of all uterine malignancies (Boutselis and Ullery, 1962, Crawford, 1959, Miller *et al* 1962, Webb, 1955) This corresponds to one sarcoma to every 10 corpus carcinomas The most recent 10 year analysis from the Danish Cancer Registry (1950–1959) revealed that among 11,216 uterine malingancies cervical carcinoma accounted for 7,590 cases, corpus carcinoma 2,977, and sarcoma 216 (including one lympho- and one reticulo sarcoma) Thus, the sarcomas constituted about 2 per cent malignant tumours of the uterus

Among the uterine sarcomas, leiomyosarcomas have been reported to make up 50 per cent (Crawford, 1959) and 75 per cent (Ober and Tovell, 1959, Webb, 1955) respectively

Table I gives an impression of the relative occurrence of the various types of uterine sarcoma

Age

Uterine sarcoma is primarily a menopausal and post menopausal disease, reaching a maximum at the end of the 5th decade, but with a wide age distribution curve However, botryoid sarcoma (a rare variant of mixed mesodermal sarcoma) is most often encountered in children and adolescents

6) aged 53	Menopause 7 years ago Metrorrhagia 3 mo ago Abdominal mass *For* 1 month	Fixed uterus s ze of nfant s *head* + parametr al nf ltra t on	Not rad cally operab le Supra ag hysterectomy X ray therapy	1 year 9 *mo* later ascites and la ge tumour masses *D ed* at end of 2 years	Le omyosarcoma *in* large f broma (sp ndlecell sarcoma)	Tumour aris ng in f bromyoma ad her ng to bladder
7) aged 43	Hypermenorrhœa for many years	Uterus med um s *zed* Small f rm in *f ltra* on on t e left	Supravag hysterectomy	Al ve and well	Hypertr myometr um F bromyomas F bromyoma with nc p ent transform *nto sarcoma*	Uterus not enlarged Sarcoma not demon*strable*
8) aged 45	Menorrhagia 1 mon h prior to adm ssion	Palpable abdom nal tumour Uterus size *of* infant s head	*Supravag* hysterectomy	Al e and well No recurrence	Hypertr myome*trium F broma* w t pronounced sarcomatous transform	Enlarged uterus w th well-def ned f bromyoma size of an orange
9) aged 46	During past 5 mo blood sta ned serous *d sch arge* and me*trorrhagia*	*Uter s size* of closed f st Ovar an endometr osis	Supravag hysterectomy X ray therapy	Al ve 5 1/2 years later	F bromyoma with *nc pient* sarcoma*tous* transform Endometriosis	Friable subserous f bromyoma size of hen s egg
10) aged 53	Menopause 6 years previously Metrorr hag a dur ng past month s	Port o vag transformed into a tumour s ze of closed f st w th a sh ny in jected s rface	D ed before treatment was inst tuted	*Died* 2 *mo* after f rst sign	Reticulosarcoma	

Table II

Case	Presenting Complaints	Physical Exam	Treatment	Course	Micr Diagdosis	Gross Appearance
1) aged 70	Fresh vaginal bleeding two weeks before *admission*	Uterus size of gooses egg, cystic ovarian tumour	Total hysterectomy bilat salpingo *oophorectomy*	Fit at end of 7 months	Pure endometrial *sarcoma*	Friable polyp, size of hen s egg, in uterus + dermoid cysts of the ovaries
2) aged 80	Metrorrhagia two weeks before admission	Debilitated, *obese*, Pyometra Uterus enlarged, parametrial masses?	Curettage Two intrauterine and vaginal applications of radium	*Died* 6 months later with large masses in the abdomen	Uterine carcinosarcoma	
3) aged 80	Vaginal spotting + brownish discharge for 6–9 months	Uterine prolapse Uterus size of closed fist	Curettage X ray therapy	Increasing abdominal tumour *Died* 21 months later	Spindle cell *and* polymorphocell sarcoma	
4) aged 78	Pelvic pain for past month	Uterus size of infant s head Palp abdominal tumour se creatinine 0 7 mg %	Supravag hysterect + *salpingo oophorect* X ray therapy	*Died* in uremia 6 *months later*	Uterine spindle cell and polymorphocell sarcoma	Uterus size of coconut with sarcoma in the posterior wall
5) aged 57	X ray castration 10 years previously for menorrhagia Now vaginal bleeding	Uterus size of grape fruit	Total hysterect + salpingo oophorect X *ray therapy*	*Died* 3 years 9 months later with *pulmonary metastases* of sarcoma	Fibromyoma with central fairly extensive transform into sarcoma	Uterus size of grape fruit + fibroma necrotic malignant tissue in the centre

Reticulin staining has sometimes been used to differentiate uterine sarcoma from anaplastic uterine carcinoma, as in the former the reticulin fibres envelop single, and in the latter groups of tumour cells (Hertig and Gore, 1957, Novak and Woodruff, 1962, Symmonds and Dockerty, 1955, Webb, 1955)

In histologically obvious cases this may be demonstrated definitely, but in questionable cases reticulin staining is of little practical value, as the collagen fibrils will stain too, and the structure of the malignant tissue is often extremely irregular

Leiomyosarcoma is histologically similar in many respects to the endometrial stromal sarcomas The presence of myofibrous stromal remnants, palisade arrangement of the tumour cells, and bizarre giant cells afford a possibility of diagnosing the leiomyosarcoma However, giant cells may also be present in the other types of tumour

Presenting complaints

The presenting complaints in uterine sarcoma are similar to those found in other uterine neoplasms In 80 per cent of the cases the initial complaint is irregular vaginal bleeding, in the form of postmenopausal bleeding or meno metrorrhagia In some cases there is purulent or serous vaginal discharge, often admixed with tissue fragments In about half the cases there is pain or a sensation of heaviness in the abdomen or pelvis (often reminiscent of men strual pain) If the sarcoma invades the bladder wall, there is vesical tenesmus frequency of micturition and in some cases urinary retention Occasionally, there may be rectal tenesmus A specific finding in children with sarcoma botryoides is an almost invariably palpable and visible tumour in the vulva

Physical findings

Gynæcological examination always shows enlargement of the uterus often to such an extent that there is a palpable abdominal mass Not infrequently the uterus will be soft to palpation, as in pregnancy

Inspection reveals in almost half the cases of endometrial sar coma in the cervical os a polypoid soft friable tumour whose

The extremely rare botryoid sarcoma is grossly polypoid, reminiscent of a bunch of grapes, and oedematous, having a surface as described above In children, it arises in the vagina, in adolescents in the cervix, and in adults in the corpus uteri

Leiomyosarcoma presents, on section, as a softer, amorphous myometrial area If the surgeon finds such a softer area in a myofibroma, he may be dealing with a secondary leiomyosarcoma As a rule, however, it is a simple necrosis, but this cannot be decided on gross inspection In such instances, microscopic examination of frozen sections during the operation is a valuable diagnostic aid

Incidentally, it is worth mentioning that the cut surface of a leiomyosarcoma resembles that of an endometrial sarcoma The differential diagnosis may be made by gross inspection, if the site of origin of the tumour can be deduced from the operative specimen

Microscopic Appearances

Uterine sarcoma shows the same histological characteristics as other malignant mesodermal tumours The neoplastic tissue is built up of numerous, more or less densely arranged, atypical cells, varying greatly in size and shape The nuclei differ in size, they are round, oval, or angular with a varying chromatin content The tumour tissue contains typical and atypical mitotic figures Some authors have used the mitotic activity as a means of grading the malignancy (Ewans, 1920, Kimbrough, 1934), a criterion which is of questionable diagnostic value

Endometrial sarcomas are of the following varieties

(1) pure sarcoma, made up exclusively of stromal tumour cells,
(2) carcinosarcoma, containing glands with carcinomatous transformation apart from the components mentioned under (1),
(3) mixed mesodermal sarcoma, containing malignant, heterologous tissue components cartilage, bone, muscle cells, and insome cases malignant uterine epithelium apart from stromal tumour cells

Novak (1962) considers rhabdomyoblasts (large spindle-shaped cells with remnants of striation) pathognomonic of this group (cf Fig 3)

Radiotherapy as the sole treatment should be reserved exclusively for patients who for any reason are unsuitable for operation At the Radium Centre, Copenhagen, radiotherapy is administered in the form of combined intrauterine and vaginal application of radium as in the treatment of corpus carcinoma

According to the literature (Boutselis and Ullery, 1962, Sternberg *et al* 1954, Symmonds and Dockerty, 1955) it is generally agreed that radiotherapy is of little value as post-operative, supplementary treatment

The 5 year survival rates clearly show that uterine sarcoma is an extremely malignant growth Collected analyses of almost 200 cases of uterine sarcoma (Webb 1955, Corshaden, 1951, Duckett *et al* 1957 Boutselis and Ullery, 1962, Crawford, 1959 Ober, 1959 Symmonds and Dockerty, 1955 Sternberg *et al* 1954) give the following impression of the prognosis Leiomyosarcoma 25 per cent survival at the end of 5 years Pure endometrial sarcoma 45-50 per cent mixed mesodermal sarcoma 25 per cent carcinosarcoma 25-30 per cent, sarcoma botryoides 30 per cent No attempts were made to correlate these percentages with any special form of treatment Two-thirds of the patients died within the first year or two

In comparison the prognosis of corpus carcinoma is appreciably better the 5 year survival rate usually being 50-60 per cent

Discussion

Preoperatively it is often difficult to diagnose uterine sarcoma In cases where a specific symptom complex is absent and where gynæcological examination does not afford any evidence of malignancy the diagnosis can be based only upon microscopic examination of a tissue specimen obtained by curettage biopsy or a Papanicolaou scraping and even then the diagnosis is established in only about two thirds of the cases (Boutselis and Ullery, 1962 Finn 1950)

The chances of arriving at a histological diagnosis preoperatively are most favourable in cases of endometrial sarcoma (in 70-80 per cent of cases) Leiomyosarcoma can only be expected to be

surface is shining and pale, often with areas of necrosis and hæmorrhagic infarcts

In the presence of pain, palpable abdominal tumour, fixation of the uterus, or parametrial infiltration, the disease must be considered far advanced and inoperable In such instances there are almost invariably blood borne metastases (predominantly in the liver and lungs) It is a matter of course to do a chest radiography before embarking upon operation on a suspicion of uterine sarcoma, as these tumours metastasize to the lungs at a very early stage

Diagnosis

The diagnosis is made preoperatively by curettage, biopsy or Papanicolaou scraping (Bruns, Porter and Mulligan, 1954) However, these procedures are not always diagnostic In Boutselis' *et al* (1962) study of 36 cases of uterine sarcoma, the diagnosis had ben made preoperatively by curettage in a total of 57 per cent, in the group of endometrial sarcomas in 12 out of 17 cases (71 per cent) The chances of demonstrating a uterine sarcoma by the Papnicolaou method are about the same as in corpus carcinoma, or about 60 per cent

The duration of complaints before the diagnosis is made has been reported to be 3–4 months by Sternberg *et al* (1954) and by Webb (1955)

Treatment and prognosis

Like sarcomas in general, uterine sarcoma spreads locally by invasion as well as by metastasization, by the blood, lymphatics, and, more rarely, by implantation If distant metastases have been ruled out, there is justification for surgery It is generally agreed that the condition requires total hysterectomy plus bilateral salpingo-oophorectomy Extended lymph node dissection in the pelvis is not indicated, as distant metastases are always present in the event of lymphogenous spread During the operation, it must be realized that often the growth of the tumour has elevated the bladder Therefore, caution must be observed in opening the peritoneum, as there is a risk of incising the bladder wall instead

Radiotherapy as the sole treatment should be reserved exclusively for patients who for any reason are insuitable for operation At the Radium Centre, Copenhagen, radiotherapy is administered in the form of combined intrauterine and vaginal application of radium as in the treatment of corpus carcinoma

According to the literature (Boutselis and Ullery, 1962, Sternberg *et al* 1954 Symmonds and Dockerty, 1955) it is generally agreed that radiotherapy is of little value as postoperative, supplementary treatment

The 5 year survival rates clearly show that uterine sarcoma is an extremely malignant growth Collected analyses of almost 200 cases of uterine sarcoma (Webb, 1955 Corshaden, 1951, Duckett *et al* 1957 Boutselis and Ullery, 1962 Crawford, 1959 Ober, 1959, Symmonds and Dockertv, 1955, Sternberg *et al* 1954) give the following impression of the prognosis Leiomyosarcoma 25 per cent survival at the end of 5 years Pure endometrial sarcoma 45-50 per cent, mixed mesodermal sarcoma 25 per cent, carcinosarcoma 25-30 per cent, sarcoma botryoides 30 per cent No attempts were made to correlate these percentages with any special form of treatment Two thirds of the patients died within the first year or two

In comparison the prognosis of corpus carcinoma is appreciably better the 5 year survival rate usually being 50-60 per cent

Discussion

Preoperatively it is often difficult to diagnose uterine sarcoma In cases where a specific symptom complex is absent and where gynecological examination does not afford any evidence of malignancy the diagnosis can be based only upon microscopic examination of a tissue specimen obtained by curettage biopsy or a Papanicolaou scraping and even then the diagnosis is established in only about two thirds of the cases (Boutselis and Ullery 1962 Finn 1950)

The chances of arriving at a histological diagnosis preoperatively are most favourable in cases of endometrial sarcoma (in 70-80 per cent of cases) Leiomyosarcoma can only be expected to be

diagnosed if the endometrium is involved in the sarcomatous lesion, or if the sarcoma arises in a submucous fibromyoma

Certain problems arise in the histological diagnosis One is the differentiation of endometrial sarcoma from sarcoma like non malignant proliferations, i e stromal hyperplasia and proliferative stromatosis (stromal endometriosis) Both tissue changes show invasion of the myometrium, at times also of the vessels Other signs of malignancy (nuclear and cellular polymorphism, hyper chromasia, mitotic abnormalities) are absent Symmonds and Dockerty (1955), who have discussed this subject in detail, relate the changes to possible inflammatory conditions or hormonal stimuli In an analysis from the Mayo Clinic, Symmonds *et al* (1957) found, on review of the histological preparations, that 16 out of 56 uterine neoplasms, primarily classified as sarcomas, had to be assigned to the group of stromal proliferations (5 cases of stromal hyperplasia, 11 of stromatosis) All these patients were in the fertile age, the clinical course was benign, and only one of the 16 succumbed as the result of spread of the tumour

Another histological problem is the differential diagnosis between carcinosarcoma and anaplastic corpus carcinoma (partially illustrated by our Case 2)

However, if the tissue specimen is of a suitable size it is usually, though not always, possible to demonstrate areas in which carcinomatous epithelial cells are detached from stromal sarcoma cells

A few authors have denied the existence of carcinosarcomas Symmonds and Dockerty (1955 b) find this group justified In their opinion, it is unlikely that cases with only a moderate dedifferentiation of the carcinomatous epithelium (Broders' grade II–III) may show, at the same time, complete anaplasia of the immediately underlying cells In nodal metastases there may be isolated carcinomatous elements, as well as isolated sarcomatous elements, or else there may be an intimate mixing of the carcinomatous and sarcomatous tumour tissue

Although our Case 1 is recorded as an example of pure stromal sarcoma, the difficulties of a definite classification are emphasized by the fact that the typical sarcomatous stroma contained scattered glands with mild precancerous changes, a possible sign of incipient, genuine carcinosarcoma (cf Fig 1)

It may be mentioned that decidua or remnants of trophoblast in menopausal women as well as cellular myofibromas have sometimes been erroneously classified as sarcomas

Of course, the pre or per-operative diagnosis of sarcomas is of significance in relation to the extent of the surgical procedure which traditionally comprises hysterectomy plu salpingo oophorectomy

In cases where surgical treatment of leiomyoma (fibromyoma) consists in supravaginal hysterectomy, the slightest suspicion of sarcomatous transformation into leiomyoma should indicate total hysterectomy There have been several instances of sarcoma development in a cervical stump (int al Case 4 in our Table II) If there is a more well founded suspicion of sarcomatous trans formation in the uterus during an operation planned as total hysterectomy, it should be supplemented by salpingo oophor ectomy

Radiotherapy is of doubtful effect It has not been demon strated whether given varities of uterine sarcoma (when dis regarding uterine lympho and reticulosarcoma) are more radio sensitive than others although in one study (Corshaden 1951) a few cases appear to have exhibited fairly marked radio sensitivity with subsidence of the tumour However, it is con cluded in all major publications that radiotherapy should not be used as the only form of treatment Most authors however prefer administering postoperative X ray or radium therapy In debili tated (cf Case 2 in our Table I) and inoperable patients, this is the only available treatment

The prognosis depends primarily upon the size of the tumour and its extent at the time of operation less upon the histological degree of malignancy Pure stromal-endometrial sarcoma has a clearly better prognosis (45-50 per cent 5 year survival) than the other varieties (25-30 per cent 5 year survival)

From the prognostic point of view there is no difference be tween carcinosarcoma and mixed mesodermal sarcoma Indeed, an extremely painstaking microscopic examination of serial sec tions is often required to demonstrate the important differential diagnostic signs single rhabdomyoblasts or other heterologous

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elements (Spechter, 1953, Sternberg *et al* 1954) This distinction is merely of scientific interest

As far as leiomyosarcoma is concerned, the prognosis is better for the secondary tumours which are frequently small and encapsulated in a leiomyoma, while the primary tumours are usually larger The original site of a leiomyosarcoma arising from a fibromyoma, may possibly have been obliterated by the rapid growth of the tumour

According to Hertig and Gore (1957) the survival rate is 3–4 times better for secondary than for primary leiomyosarcoma

The more favourable prognosis of the small, secondary leiomyosarcomas is also evident from the tabulation of the present cases

Occasionally, one may be faced with uterine sarcomas which at the time of operation are so extensive and so lacking in specific histological criteria that it is impossible to decide whether they have arisen primarily in the endometrium, myometrium, or perhaps—very rarely—are metastases

In such cases the prognosis is the worst possible

SUMMARY

The present paper gives a survey of the literature on the classification, incidence, age distribution, ætiology, pathology, presenting complaints, diagnosis, treatment, and prognosis of uterine sarcoma

The data for 10 patients with uterine sarcoma are tabulated Two of the cases, who had endometrial sarcoma, are described in more detail

Case Reports

Case 1 (Case 1, Table II)

A 70-year-old woman previously admitted with atherosclerotic heart disease obesity, and acute gangrenous cholecystitis (treated by cholecystectomy) No other major illnesses Gynæcological history normal periods regular, 6 normal deliveries No pelvic infections or abortions menopause at 52

Her present illness had started two weeks prior to admission with vaginal bleeding, fairly profuse for 2 days, but during the past few days only in the form of oozing No disturbances of urination or defaecation

Gynæcological examination Inspection revealed no abnormality

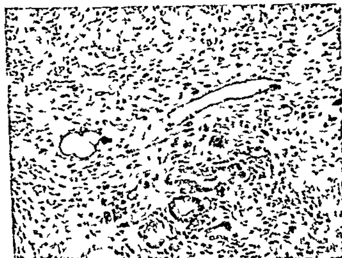


Fig 1 Endometrial stromal sarcoma (Case 1)

Bimanual palpation revealed a normal cervix merging into an approximately tangerine-sized round firm tumour in the midline Anteriorly on the right a slightly smaller round smooth adnexal tumour which was of a somewhat softer consistency Curettage yielded fairly ample hyperplastic rather pale curettings suggestive of malignancy

Microscopic examination (Fig 1) showed an endometrial diffuse stromal sarcoma in the corpus mucosa with pronounced hyperplasia and some glandular atypia Indication for inferior median laparotomy

The operation comprised total hysterectomy plus bilateral salpingo-oophorectomy The uterus was soft and the size of a goose s egg When it was cut its lumen was found to be considerably dilated by a polyp as large as a hen s egg arising from the right cornu by a short pedicle as thick as a lead pencil The polyp was quite soft and so friable that it burst upon the lightest pressure The right ovary was transformed into a tangerine-sized dermoid cyst the left one into a tangerine-sized simple cyst with calcification Fallopian tubes normal

The postoperative course was smooth and uneventful apart from mild paralytic ileus Six months after the operation the patient s doctor reported that she was fit and without any clinical sign of recurrence

Microscopic diagnoses

- *endometrial sarcoma* (endometrial polyp of the corpus with extensive endometrial stromal sarcoma moderate glandular hyperplasia and atypia as well as profuse hæmorrhage and necrosis)



Fig 2 Carcinoma sarcoma (Case 2)

- atrophic corpus endometrium with pronounced menopausal changes of the mucosa,
- severe myometrial hypertrophy,
- mild internal endometriosis in the corpus
- tubes normal
- dermoid cyst with calcification of the left ovary,
- *dermoid cyst of the right ovary,* with fibrosis and calcification (sd *Svend* Petri)

Case 2 (Case 2 in Table II)

An 80-year-old woman with a history of cholecystectomy and operation for genital prolapse No other major illnesses Five normal deliveries Menopause without complaints During the past few years the patient had become increasingly atherosclerotic senile with impaired memory tired

Her present illness had started 12 days before admission as a sudden brownish vaginal discharge decreasing after 2 days but replaced by a slight, constant, bright vaginal bleeding

Gynaecological examination Inspection showed the vulva to be normal Scars in the anteiror and posterior walls of the vagina left by the colporrhaphy Ample oozing of pus from the cervical canal and polyp like tumour tissue in the os

Bimanual examination Cervix and corpus slightly to moderately enlarged regular not tender No definite parametrial masses Further details could not be assessed owing to the patient s obesity and inability to relax Uterus 7 cm



F g 3 Example of rhabdomyoblast

deep Large fragments of tissue removed from the cervical canal and curet tings from the corpus were sent for microscop c study

Laboratory invest gations Hb 84–80 % E S R 41 26 mm urine no al bumin or sugar Serum creatinine 0 9 mg 100 ml

E C G No abnormal ty Chest rad ography Ectas a of the aorta signs of past pleurisy

M c oscop c d agnos s (F g 2)

carc nosa coma of the uterine corpus (or cerv x)

(Med um-sized pole curett ngs from the corpus showing adenocarcinoma of the corpus or cervix uniform sarcomatous stromal proliferat on severe subacute-chronic s mple nflammatory changes necrotic ulceration w th f brinopurulent coating and remnants of old hæmorrhage) (sd S end Petri)

As the pat ent was old an deb l tated w th general zed atheroscleros s and moderate obes ty operation was not performed

Transferred to the Rad um Centre Copenhagen where she had two intrau terine and vag nal appl cations of rad um Feel ng well on d scharge

S x months later her own doctor reported that she had d ed in her home after stead y deteriorat on w th widespread tumour masses in the abdomen (no autopsy)



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HORMONE EFFECTS ON CARCINOMA OF THE HUMAN UTERINE BODY STUDIED IN ORGAN CULTURE

A Preliminary Report

BY

R STAFFAN B NORDQVIST

The finding that mammary and prostatic cancer may regress during hormonal therapy has stimulated the interest in similar therapeutical approaches to malignant tumours arising in other endocrine-dependent tissues One such tumour is cancer of the uterine body Patients with this cancer often show symptoms of obesitas, hypertension, hirsutism, and diabetes Among other things, hyperœstrogenism, endometrial hyperplasia, hyperplasia of the ovarian stroma, and diffuse thecomatosis have been discussed as ætiological factors (Kistner, 1962 Novak and Yui, 1936, Wilson, 1962) Sherman and Woolf (1959) found a high percentage of Leydig-cell hyperplasia and elevated LH-levels in patients with cancer of the uterine body, but only in few postmenopausal women without endometrial cancer or hyperplasia The LH levels were reduced to below normal in all cases after bilateral oophorectomy

If endocrine factors are important for the ætiology of endometrial cancer, a hormonal dependency of the cancer cells might be expected to persist for a shorter or longer time More or less successful therapeutical trials with progesterone or progesterone derivatives have been reported at endometrial hyperplasia, carcinoma in situ, and invasive and metastasizing carcinoma of the

uterine body (Kelley and Baker, 1961, Kennedy, 1963 Kistner 1959, 1962 Varga and Henriksen, 1961) These series are clinical studies of patients with or without previous surgical treatment or radiological treatment or both

In the present investigation, the mode of reaction of carcinoma of the uterine body to different endocrine stimuli was studied in organ cultures *in vitro* At our laboratory endocrine effects on cell cultures from human genital tumours have previously been described (Kullander and Kallen, 1961 Rohl, 1959) These experiments were made on plasma clot cultures, where cells grew as a mat and growth could be studied continuously for a period of one to two weeks When this type of cultures are prepared from normal endometrium and endometrial cancer, a strong fibrinolysis occurs (Kullander and Kallen, 1961) Therefore the plasma clot culture method could not be used in my study In stead cultures were prepared as sponge matrix organ cultures (Leighton 1951)

Material and methods

Twelve uterine body tumours were examined 11 of them were adenocarcinomas the twelfth was a mixed tumour of a rhabdo myosarcoma type Specimens were obtained by curettage and were placed directly in Tyrode balanced salt solution They were cut into small fragments one or two mm in diameter Some of the specimens were fixed immediately in order to serve as basis of comparison at the later analysis of the sectioned cultures Two fragments were put on one piece of gel foam (Spongostan[R]) Two gel foam pieces were placed in a Carrel flask containing 1 5 ml of 10 % adult human blood donor serum in Parker 199 The flasks were divided into five groups two in each Hormones were added from alcoholic stock solutions

Group 1 Control cultures only alcohol added
Group 2 Œstrogen cultures 3 mg œstrone/ml added
Group 3 Progesterone cultures 1 6 mg progesterone/ml added
Group 4 Progesterone cultures 16 mg progesterone/ml added
Group 5 Androgen cultures 5 mg androsterone/ml added

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Table I *Total Material*

Case		Age	Meno-pause Age	Parity	Classification of Tumour		Control	Œstrogen	Prog 8 µg/ml	Prog 80 µg/ml	Androgen
	S P	55	—	0	High differentiation	s	+++	+++	+++	o	+
					partially papillary	d	o	—	o		
						m	+	o	+		
I	L.A.	74	45	0	Low differentiation	s	+++	+++	+++		+
					squamous metaplasia	d	o	+	+		
						m	o	+	+		
II	A P	68	50	2	High differentiation	s	+++	++−	+++	+++	+++
						d	o	o	o	o	o
						m	o	+	+	o	o
V	A.S	48	—	1	Low differentiation	s	+++	+++	++	+	+++
					squamous metaplasia	d	o	+	o		+
						m	o	o	o		o
V	A.M	52	49	4	High differentiation	s	+++	+++	+	o	+++
						d	o	o			o
						m	o	o			o
VI	A A	83	48	0	High differentiation	s	+++	++	++	o	++
						d	—	—	—		o
						m	o	o	o		o
VII	B B	75	48	0	Low differentiation	s	+++	+++	++	+	+++
					papillary growth and	d	o	o	o		o
					necroses	m	o	+	o		o
IX	V T	68	48	4	Low differentiation	s	+++	+++	+++	+	++
						d	o	o	+		o
						m	+	+	o		o
X	F N	61	57	1	Low differentiation	s	+++	++	+++	+	+
					partially papillary	d	o	o	o		
						m	o	o	+		
XI	G G	64	42	0	Low differentiation	s	+++	++	+++	o	++
						d	o	o	o		o
						m	o	o	o		o
XII	A A	48	—	3	High differentiation	s	+++	++	+++	o	+++
					partially papillary	d	o	—	—		+
						m	o	o	o		o

+++ Excellent survival no necroses
++ Good survival occasional necroses
+ Poor survival advanced *necrosis*
o No survival total necrosis

s Survival
d Differentiation compared with that of the original tumour O same + higher — lower
m Mitoses o none visible + visible

The final alcohol concentration in all groups was 0.5 %. This is equivalent to 15 µg/ml Œstrone, 8 and 80 µg/ml progesterone and 25 µg/ml androsterone. The flasks were incubated at 37.5° C. The gel foam pieces were removed after seven or eight days, and fixed in Bouin's fluid, embedded in paraffin-wax, sectioned serially at eight or ten microns, and stained with hæmatoxylin and eosin.

At analysis of the sections, survival was scored according to the following four groups:

+++ Excellent survival, (*e.g.*, Fig. 5)
++ Good survival, occasional necroses, (*e.g.*, Fig. 6)
\+ Poor survival, advanced necrosis, (*e.g.*, Fig. 3)
o Total necrosis, (*e.g.*, Fig. 8)

Further, the slides were studied for the presence of mitoses, *and an attempt was made to judge the degree of differentiation of* the tumours after culturing compared with that of the original tumours.

Results and discussion

It was possible to study 11 tumours more closely. The rhabdomyosarcoma degenerated completely in all flasks, therefore this tumour will not be discussed.

The observations made are summarized in Table I and II. In *many cultures, stroma cell degeneration was seen, apparently in*dependent of glandular survival (Fig. 1). As is apparent from Table II, survival in control cultures was excellent in all tumours. With œstrogen and weak progesterone treatment, slightly poorer survival was seen. With strong progesterone treatment, advanced or total necrosis was found in all tumours but one — case III A R, a highly differentiated adenocarcinoma (Fig. 2). One of the strong progesterone cultures could not be studied owing to a technical mishap. With androsterone treatment, survival was found to be intermediate between weak and strong progesterone treatments.

Definite mitosis was seen in control cultures of two tumours, and in œstrogen cultures of four tumours and weak progesterone cultures of four tumours.

Table I *Total Material*

Case	Age	Menopause Age	Parity	Classification of Tumour		Control	Œstrogen	Prog 8 µg/ml	Prog 80 µg/ml	Androgen
I SP	55	—	o	High differentiation partially papillary	s	+++	+++	+++	o	+
					d	o	—	o		
					m	+	o	+		
II LA	74	45	o	Low differentiation squamous metaplasia	s	+++	+++	+++		+
					d	o	+	+		
					m	o	+	+		
III AR	68	50	2	High differentiation	s	+++	+++	+++	+++	+++
					d	o	o	o	o	o
					m	o	+	+	o	o
IV AS	48	—	1	Low differentiation squamous metaplasia	s	+++	+++	++	+	+++
					d	o	+	o		+
					m	o	o	o		o
V AM	52	49	4	High differentiation	s	+++	+++	+	o	+++
					d	o	o			o
					m	o	o			o
VI AA	83	48	o	High differentiation	s	+++	++	++	o	++
					d	—	—	—		o
					m	o	o	o		o
VII BB	75	48	o	Low differentiation papillary growth and necroses	s	+++	+++	++	+	+++
					d	o	o	o		o
					m	o	+	o		o
IX VT	68	48	4	Low differentiation	s	+++	+++	+++	+	++
					d	o	o	+		o
					m	+	+	o		o
X EN	61	57	1	Low differentiation partially papillary	s	+++	++	+++	+	+
					d	o	o	o		
					m	o	o	+		
XI GG	64	42	o	Low differentiation	s	+++	++	+++	o	++
					d	o	o	o		o
					m	o	o	o		o
XII AA	48	—	3	High differentiation partially papillary	s	+++	++	+++	o	+++
					d	o	—	—		—
					m	o	o	o		o

+++ Excellent survival no necroses
++ Good survival occasional necroses
+ Poor survival advanced necrosis
o No survival total necrosis

s Survival
d Differentiation compared with that of the original tumour O same + higher — lower
m Mitoses o none visible + visible

Table II *Total Material* (11 Cases)

Survival	Control	Œstrogen	Prog 8 γ/ml	Prog 80 γ/ml*	Androgen
+++	11	7	7	1	5
++		4	3		3
+			1	4	3
0				5	
Mitoses +	2	4	4		
Differentiation +		2	3		2
Differentiation —	1	3	1		

* only 10 cases

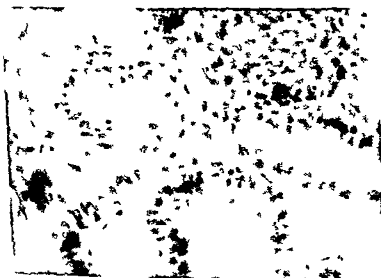
Case XII A A is of especial interest (Figs 4—8) The original tumour was a highly differentiated papillary adenocarcinoma with numerous mitoses The same picture was seen in the control cultures, whereas the œstrogen cultures showed growth of a cancer of apparently lower differentiation and occasional necroses (++) In sharp contrast to this, glandular structures with a high columnar epithelium and signs of secretion were found in the weak progesterone cultures A similar picture was seen in the androgen cultures, although the cells were then more cubical In the strong progesterone cultures, necrosis was total

In some instances, the degree of differentiation of the tumours seemed to have changed during culturing as indicated above Thus, a higher differentiation was seen in two œstrogen cultures, three weak progesterone, and two androgen A lower differentiation was found in one control culture three œstrogen cultures and one weak progesterone culture The significance of this observation cannot so far be evaluated Of course different parts of a tumour may show varying degree of differentiation, but it must be stressed that both explants and original preparations were in all instances made from the same piece of the tumour, approximately one cm in diameter

No correlation could be found between, on the one hand, the endocrine responsiveness of the tumour in culture, and on the other, the degree of differentiation, time of debut of symptoms



F g Ca e III A R Œstrogen culture Excellent surv val ( ) No change n d fferentiat on M toses present Stroma cell d sappea ance Ma nif cat on Appr oo



F g 2 Ca e A R P oge te one culture 80 µg ml Ex ellent surv val ( ) No hange in d ffe entiat on No m to es Stroma cell d sappea an e Magnifica on Appr 250

Fig 3 Case X E N Androgen culture Poor survival advanced necrosis (+) Magnification Appr 100 ×

Fig 4 Case XII A A Original tumour Well differentiated adenocarcinoma Magnification Appr 250 ×



Fig 5 Case XII A A Control culture Excellent growth (+ +) No change in differentiation No mitoses Magnification Appr 250 ×

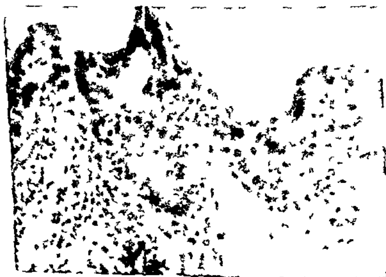


Fig 6 Case XII A A Œstrogen culture Good survival occasional necroses (+) Lower differentiation No mitoses Magnification Appr 250

Fig 7 Case XII A A Progesterone culture 8 µg/ml Excellent sur al (+++) H gh columnar ep thelium vith ev dence of secretion h gher differentiat on No m toses Magnification Appr 250 ×

F g 8 Case XII A A Progesterone culture 80 µg ml Total necros s Magn f cat on Appr 250 ×

after menopause, age of the patient, presence of myoma, or use of hormonal substitutional therapy This is in accordance with the clinical experience reported Kennedy (1963), however, points out that slowly growing cancer reacts better on therapy with Delalutin (17 alpha hydroxy-progesterone 17 n caproate) than does rapidly growing cancer Varga and Henriksen (1961) found in 13 patients, treated with large doses of Delalutin without previous surgical or radiological therapy without exception gross clinical changes consistent in all instances manifested as reduction in size of the corpus uteri clearing of malodorous discharge and decrease in amount of bleeding On histopathological evaluation five of these evidenced tumor alterations predominating as secretory or acanthomatous conversion separately or in combination In one there was no residual tumor in the hysterectomy specimen" The authors present two theories concerning the mode of action of Delalutin 1 Via the hypophysis "as an antiluteinizing hormone suppressant" 2 Directly on the endometrium either non metabolized or as break-down products Unpublished data are said to favour the latter theory These authors (1964) have also given Delalutin to patients with other malignant genital tumours such as squamous cell and adenocarcinoma of the cervix ovarian cancer sarcoma of the uterine body and choriocarcinoma without finding any tumouricid or tumouristatic effect Kennedy (1963) found objective regress in 8 of 23 patients with cancer of the uterine body and Kelley and Baker (1961) in 6 of 21 and a duration of the regress of 9 months to 4½ years Kistner (1959) has with good success given progesterone to patients with hyperplastic endometrium or carcinoma *in situ*

In the present study progesterone in the concentration of 8 µg/ml provoked advanced necrosis in only one instance With a concentration of 80 µg/ml the effect was more pronounced—excellent survival present only in one instance the other nine showing advanced or total necrosis This might suggest that most uterine body cancers will regress on progesterone treatment if only concentrations high enough can be reached in the endometrium The results also suggest that different cancers need different high concentrations The possibility cannot be excluded

however, that the necessary concentrations will sometimes be so high as to produce a general toxic effect *in vivo*

Kennedy's (1963) statement, "Progestogens have a definite role in the therapy of advanced or recurrent carcinoma of the endometrium", seems to be supported by this study and stimulates further development of the method, whose aim is to serve as a screening test for dividing cancers of the uterine body into groups sensitive and non-sensitive to hormonal treatment

SUMMARY

A preliminary report is given of endocrine effects on human uterine body cancers, studied in organ culture A sponge-matrix culture method was used, and the effect of added œstrone, progesterone, and androsterone studied Twelve tumours were cultured—11 adenocarcinomas survived in control cultures Marked regressive changes were seen after addition of progesterone in a concentration of 80 μg/ml Progesterone in a concentration of 8 μg/ml and androsterone in a concentration of 25 μg/ml produced less marked effects The results are discussed in the light of clinical studies published by others

Acknowledgment

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PERIPHERAL CIRCULATION DURING NORMAL PREGNANCY

BY

SVEN SPETZ

During pregnancy important cardiovascular adaptations occur Some of these have been rather extensively studied, such as the increase of cardiac output and the rise in plasma volume (Dieckmann and Wegner, 1934 Werko, Bucht, Lagerlöf, and Holmgren, 1948 Kjellberg Lonroth, Rudhe, and Sjostrand 1950 Hamilton, 1950, Gemzell, Robbe, and Sjöstrand 1954 Gylling, 1961)

The present series of studies deals with certain aspects of peripheral circulation during pregnancy Special interest was devoted to the circulation in skeletal muscle and skin since it is known that these tissues show pronounced vascular reactivity (Barcroft and Swan 1953 Folkow 1955 Barcroft, 1963) In this paper the forearm blood flow was examined during normal pregnancy In a second study the capillary filtration rate in the forearm of normal pregnant women will be described Finally in a third paper, peripheral blood flow and capillary filtration rate will be analyzed in diabetic patients and in pregnancies complicated by toxæmia Such aspects of peripheral circulation during pregnancy have formed the subject of only a limited number of investigations However studies of this kind might elucidate changes in peripheral resistance to blood flow in the distribution of nutritional blood flow in the capillary network, and in the net transfer of fluid across the capillary membranes Information about such important peripheral vascular functions would aid in the understanding of cardiovascular hæmodynamics during pregnancy

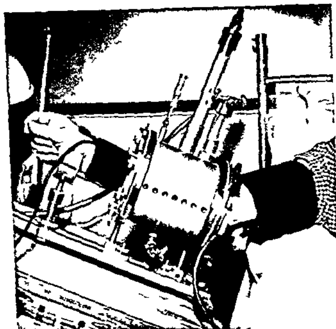


Fig 1 Plethysmograph ready for use

tremity will lead to a progressive increase of volume, due to the accumulation of blood in the vascular bed At a low occlusion pressure interference with the arterial inflow is negligible Therefore, it can be assumed that the rate of volume increase following occlusion reflects the rate of arterial inflow It is well known that the rise in limb volume reflects the arterial inflow only during the first few seconds after occlusion When venous pressure starts to rise the arterio venous pressure difference decreases and hence the inflow decreases When the venous pressure exceeds the occlusion pressure blood escapes under the occluding cuff

The plethysmograph The design of the plethysmograph is seen in Fig 1

The forearm is surrounded by a rubber sleeve made from thin latex rubber At both ends this sleeve is continued by rubber diaphragms, made from 3 mm thick soft rubber These sleeves

Previous studies on changes in peripheral circulation during pregnancy are somewhat conflicting Huchard (1910) assumed that peripheral vasoconstriction was necessary to meet the increasing demands of the uterus and fœtus for blood Quantitative measurements on the rate of blood flow have been presented by Abramson, Flachs, and Fierst (1943) In the majority of their cases no definite change in blood flow could be established during pregnancy Contrary to this Burt (1950) noted an increase in forearm and hand blood flow in the latter half of pregnancy However, the most extensive study seems to be that by Herbert, Banner, and Wakim (1954, 1958) They examined a large number of pregnant women and noticed a decrease in forearm blood flow up to the middle of the gestation period From the 20th week there was an increase in blood flow, reaching a maximum at about one month before delivery Then the rate of blood flow gradually declined

Material

Twenty-seven pregnant women were studied In most cases investigation was started at their first visit to the hospital when the pregnancy was confirmed This was usually at the 11th–12th week of gestation The age of the patients varied between 20 and 40 years Most of them (20) had not been pregnant before, 7 had had one previous normal pregnancy and delivery The subjects were followed at intervals of 2–3 months 4 separate studies were made on each of them

Twenty one non-pregnant women were used as controls Their ages varied between 17 and 31 years None of these subjects had been pregnant Each of them was studied once only and under experimental conditions identical with those of the pregnant group

Methods

General principles The rate of forearm blood flow was measured by venous occlusion plethysmography For general information regarding the underlying principles see Barcroft and Swan (1953) A sudden occlusion of the venous return from the ex-

and after the plethysmograph had been fitted to the right forearm, she was allowed to rest for at least 30 minutes before any measurements were made The temperature of the plethysmograph was maintained at 36°C, a level at which most patients reported thermal comfort

Before actual measurements of blood flow were performed the following tests were made When the plethysmograph was con nected to the volume recorder, arterial pulsations should be present in the record The volume of the limb had to remain constant

The arterial blood pressure was determined in the left arm by the conventional sphygmomanometer cuff method and ausculta tion of Korotkov s sound For blood flow determination the pres sure in the proximal cuff was increased to 40 mm Hg throughout the study This pressure, being always lower than the diastolic blood pressure, was high enough to cause a linear increase of limb volume of sufficient length to permit calculation of inflow rate The 2 cuffs on the right arm of the subject were connected to separate pressure reservoirs, in which the pressure could be set at any predetermined level During blood flow recording the distal cuff was inflated to a supra-systolic pressure During each blood flow determination both cuffs were momentarily inflated to the predetermined pressure levels, switching three way taps con necting them to the pressure reservoirs These pressures were then maintained for 4 to 5 seconds As a routine 10 measurements were made each of them separated by an interval of at least one min ute From the slopes on the plethysmograms the rate of arterial inflow was determined and a mean value calculated

Simultaneous measurements of arterial blood pressure and the rate of forearm blood flow make calculations of forearm resistance to blood flow in peripheral resistance units (PRU) possible, ac cording to Green, Lewis, and Nickerson (1944) Functional mean arterial pressure was taken as the diastolic pressure plus 1/3 of the pulse pressure

In order to determine the maximal blood flow capacity of the forearm reactive hyperæmia was induced This was achieved by the combined effects of 5 minutes arterial occlusion of increasing the water temperature in the plethysmograph to 42 C and of muscular work having the subjects perform rapid and strong

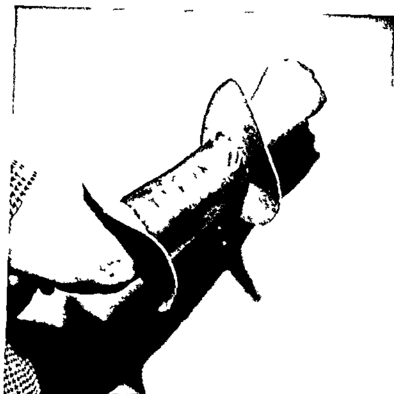


Fig 2 The thin rubber sleeve on the forearm The rubber diaphragms are seen at both ends of the sleeve

were available in varying sizes so that a suitable set can be selected for each subject (Fig 2)

It is necessary that these sleeves fit closely but not tightly If too tight they interfere with venous circulation, if too loose the recording of blood flow is not possible Both these factors are easily checked while performing the actual measurements of blood flow

With a 6 cm wide sphygmomanometer cuff on the wrist the circulation through the hand can be interrupted during the short periods of recording An ordinary sphygmomanometer cuff (12 cm wide) is applied to the upper part of the arm

Experimental conditions The rate of blood flow is influenced by a large variety of factors and this necessitates strictly standardized conditions The room was thermostatically maintained at 22°C and kept in semi darkness The patient was kept in bed,

The arrows indicate the moment at which the sphygmomanometer cuff was inflated to a pressure of 40 mm Hg A sudden increase in limb volume occurs due to a simultaneous displacement of tissue into the plethysmograph Thereafter there is a continuous increase of limb volume and the rate of arterial inflow is calculated from this linear slope during the first seconds after occlusion

Statistics For calculation of arithmetic mean, standard deviation, confidence limits, and regression line conventional statistical methods have been applied (Hald, 1951) The significance of differences between groups was tested by the t test A significance level of 5 per cent was chosen for the design of the experimental model to be tested with statistical analysis

In the statistical analysis of the relations between time of gestation and forearm blood flow and peripheral resistance, respectively, certain assumptions will be made In this work the regression functions (relations) are assumed to have the following properties

1 The only period of importance is that between the 11th and 40th week of pregnancy and no extrapolation in any direction is necessary

2 During pregnancy there are considerable changes in plasma volume and cardiac output (for references see above) It may be assumed that the increase in these parameters follows an exponential function Herbert, Banner, and Wakim (1954, 1958) have demonstrated that the increase in peripheral blood flow parallels the increase in plasma volume and cardiac output It may further be assumed that the peripheral resistance must decrease, provided that there is no major change in blood pressure

A simple regression function satisfying the above mentioned properties for the relation between duration of pregnancy and forearm blood flow is the exponential function

$$(1\ 1) \quad P = \gamma \cdot e^{\beta t} \quad \beta \geq 0 \quad 11 \leq t \leq 40$$

where the variable P denotes forearm blood flow and the variable t the duration of pregnancy

For the relation between the duration of pregnancy and the regional vascular resistance the following function complies with the above mentioned properties

$$(1\ 2) \quad PRU = \alpha \cdot e^{-\delta t} \quad \delta \geq 0 \quad 11 \leq t \leq 40$$

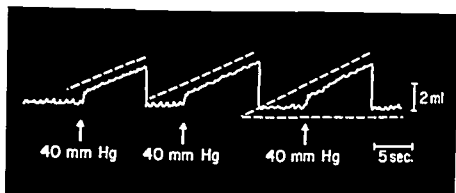


Fig 3 A series of plethysmograms from a subject in the control group The blood flow was 3 6±0 8 ml/min ×100 ml For further information see text

contractions of the hand during the last 30 seconds of arterial occlusion The arterial occlusion was obtained by suddenly inflating the proximal sphygmomanometer cuff to pressures around 250 mm Hg For measuring the reactive hyperæmia the pressure in this cuff was momentarily lowered to 40 mm Hg and an initial arterial inflow curve recorded After deflation repeated determinations of flow were performed Two such hyperæmia tests were carried out 'Maximal blood flow capacity' was taken as the highest peak flow recorded during the hyperæmia period

Hand blood flow was measured in 2 patients during pregnancy in order to clarify the magnitude of skin blood flow The experimental conditions were the same as above In one subject 3 separate studies were made, in the other 4

In 4 pregnant subjects forearm and hand blood flow were simultaneously recorded during warming the legs of the subjects in order to study the effects of thermal stimulation on the peripheral blood flow

The plethysmograph was calibrated from a 2 ml syringe on top of the plethysmograph The volume recordings were carried out on sooted paper by means of a piston recorder (Palmer)

The water level in the plethysmograph was kept constant in all experiments As the volume of the plethysmograph was known, the limb volume could easily be calculated by measuring the water content

The plethysmogram Fig 3 shows a series of plethysmograms

The arrows indicate the moment at which the sphygmomanometer cuff was inflated to a pressure of 40 mm Hg A sudden increase in limb volume occurs due to a simultaneous displacement of tissue into the plethysmograph Thereafter there is a continuous increase of limb volume and the rate of arterial inflow is calculated from this linear slope during the first seconds after occlusion

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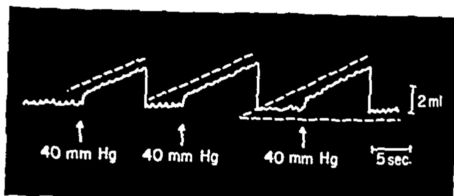


Fig 3 A series of plethysmograms from a subject in the control group The blood flow was 3 6±0 8 ml/min ×100 ml For further information see text

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The water level in the plethysmograph was kept constant in all experiments As the volume of the plethysmograph was known, the limb volume could easily be calculated by measuring the water content

The plethysmogram Fig 3 shows a series of plethysmograms

Table I

Number	Duration of Pregnancy in Weeks	Resting Forearm Blood Flow ml/min. x 100 ml Mean ± Standard Deviation	Peripheral Vascular Resistance in PRU	Maximal Blood Flow Capacity ml/min. x 100 ml	Percentage of Resting Blood Flow to Maximal Blood Flow Capacity
1	12	2.1 ± 0.14	44	33.5	6.3
	18	1.5 ± 0.20	61	32.0	4.7
	29	2.6 ± 0.33	33	32.0	8.1
	38	11.7 ± 1.00	7	30.0	39.0
2	16	4.0 ± 1.14	23	23.0	17.4
	24	3.6 ± 0.64	24	32.0	11.2
	32	11.7 ± 1.29	8	33.8	34.6
	39	15.3 ± 1.77	1	31.5	48.6
3	11	1.9 ± 0.22	44	29.5	6.4
	22	2.8 ± 0.26	29	40.0	7.0
	31	7.9 ± 1.23	11	45.0	17.6
	37	8.4 ± 0.95	10	37.3	22.5
4	17	3.1 ± 0.37	29	18.8	16.5
	23	4.6 ± 0.35	20	21.0	21.9
	29	6.7 ± 0.88	13	27.4	24.5
	38	16.6 ± 1.35	6	31.6	52.5
5	17	1.6 ± 0.28	61	24.3	6.6
	23	2.9 ± 0.37	29	26.2	11.1
	28	5.5 ± 0.58	17	26.2	21.0
	33	9.6 ± 0.89	10	–	–
6	12	1.7 ± 0.26	49	29.5	5.8
	21	2.0 ± 0.24	44	25.3	7.9
	28	3.4 ± 0.24	25	39.0	8.7
	36	9.7 ± 0.66	9	26.5	36.6
7	12	3.4 ± 0.24	26	29.5	11.5
	20	6.1 ± 0.62	13	27.6	22.1
	28	8.8 ± 0.60	9	39.2	22.4
	39	12.4 ± 1.17	7	36.4	34.1
8	11	3.4 ± 0.22	29	27.8	12.2
	18	3.4 ± 2.41	26	28.1	12.1
	26	7.8 ± 1.44	11	33.7	23.1
	37	19.6 ± 1.48	5	37.5	52.3
9	12	1.2 ± 0.14	75	27.8	4.3
	22	5.0 ± 0.39	20	28.4	17.6
	29	4.3 ± 0.60	21	23.7	18.1
	39	11.6 ± 1.21	9	26.4	43.9
10	12	1.5 ± 0.22	63	21.4	7.0
	20	1.8 ± 0.10	50	29.3	6.1
	30	9.4 ± 1.30	10	28.9	32.5
	39	10.1 ± 1.12	9	29.8	33.9

where the variable PRU denotes the peripheral vascular resistance in the forearm

The constants α, β, γ, and δ are calculated from the single experimental observations

If the relations are non-linear and fit these exponential functions transformation of the variables or any of them will give the regression function a linear form If such linear functions for the relations can be established, the coefficients of regression, denoted by β and δ will give an expression for the intensity with which the peripheral blood flow and the peripheral vascular resistance changes with increasing length of gestation

The confidence limits for the coefficient of regression can be calculated, which gives the limits between which this value may vary

By logarithmic transformation of (1 1) and (1 2) the following is obtained

(1 3) $y = \log_e P = \log_e \gamma + \beta t, \ \beta \geqq 0, \ 11 \leqq t \leqq 40$

and

(1 4) $z = \log_e PRU = \log_e \alpha - \delta t, \ \delta \geqq 0, \ 11 \leqq t \leqq 40$

The function (1 3) indicates that there is a linear relation between the logarithm for P and t, and the function (1 4) shows that this is also the case for PRU and t The logarithmic transformation is therefore limited to the P and PRU variables

The constants α, β, γ, and δ are calculated from the logarithmic values of the experimental observations by the method of least squares To test whether the linear functions fit the material and consequently whether the experimental model is suitable, the variances must be tested with Bartlett s test, and then the linearity examined with an analysis of variance

Results

Table I illustrates the results obtained in 10 subjects during pregnancy concerning resting forearm blood flow, peripheral resistance, peak blood flow during reactive hyperæmia, and resting blood flow expressed as a percentage of 'maximal blood flow capacity" Because of limitation of space the results from the

Table II

Duration of Pregnancy in Weeks	Number of Observations	Mean of Observed Values of Blood Flow ml/min x 100 ml	Mean of the $\log_e$ Values of Blood Flow	Standard Deviation of the $\log_e$ Values
11–13	14	2 1	0 67	0 34
14–16	6	2 7	0 91	0 50
17–19	8	3 3	0 94	0 74
20–22	11	3 3	1 10	0 47
23–25	8	3 4	1 10	0 51
26–28	6	6 0	1 69	0 52
29–31	9	6 9	1 85	0.46
32–34	9	7 5	1 84	0 69
35–37	10	10.4	2 29	0 31
38–40	11	12 3	2 46	0 35

In Fig 5 the mean values for blood flow are plotted against the duration of pregnancy The shaded area indicates the mean value and the 95 per cent confidence limits for the mean in the non-pregnant group

The increase in blood flow is quite impressive after the 25th week of gestation At term the blood flow has, on an average, reached a value of 12 3 ml/min ×100 ml The difference between this value and that found in the non pregnant women is statistically significant (t=10 2, df/degrees of freedom/=30) The difference between the mean value for early pregnancy (11th–13th week of gestation) and that for the non pregnant control group, on the other hand is not significant (t=1 69 df=33) The variances in the groups were tested by an F test and no different between the variances was found

The relation between $\log_e$ P and t (Fig 6) was calculated from the experimental observations

$y = \log_e P = 0\ 069\ t - 0\ 280$ according to (1 3)

or $P = 0\ 76\ e^{0\ 069\,t}$ according to (1 1)

The residual variance in y is 0 23 and the total variance in y is 0 62 The variances at the *different* periods of pregnancy were tested and were found to be independent of the period of gestation

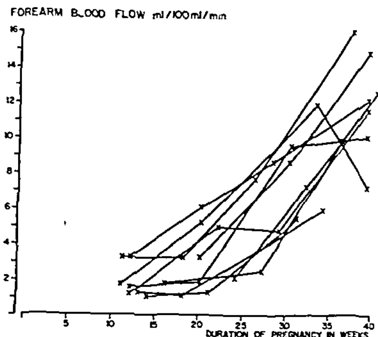


Fig 4 Blood flow in relation to duration of pregnancy in 10 subjects

other subjects have been omitted in this table, but the results presented are representative of the whole series

Resting forearm blood flow In Fig 4 the results from 10 consecutive subjects are seen

It is clear from this figure that there is in general a considerable increase in the rate of resting forearm blood flow, which starts at about the 20th week of pregnancy and goes on until term It is also obvious that the magnitude of the blood flow differs markedly among the patients In order to clarify the trend, the pregnancy has been divided in three-week periods The length of pregnancy *has been calculated from the first day of the last period* *The mean* values calculated include all observations made in each three-week period on the whole series studied

Table II shows the number of observations in each three-week period, the mean values of blood flow, means of the logarithmic values for blood flow, and standard deviation of the logarithmic values In the non pregnant group the mean value for blood flow was 2 8 ml/min × 100 ml, the logarithmic mean value was 0 91 and the standard deviation 0 45

Table II

Duration of Pregnancy in Weeks	Number of Observations	Mean of Observed Values of Blood Flow ml/min. × 100 ml	Mean of the $\log_e$ Values of Blood Flow	Standard Deviation of the $\log_e$ Values
11–13	14	2 1	0 67	0 34
14–16	6	2 7	0 91	0 50
17–19	8	3 3	0 94	0 74
20–22	11	3 3	1 10	0 47
23–25	8	3 4	1 10	0 51
26–28	6	6 0	1 69	0 52
29–31	9	6 9	1 85	0.46
32–34	9	7 5	1 84	0 69
35–37	10	10 4	2 29	0 31
38–40	11	12 3	2.46	0 35

In Fig 5 the mean values for blood flow are plotted against the duration of pregnancy The shaded area indicates the mean value and the 95 per cent confidence limits for the mean in the non-pregnant group

The increase in blood flow is quite impressive after the 25th week of gestation At term the blood flow has, on an average, reached a value of 12 3 ml/min × 100 ml The difference between this value and that found in the non pregnant women is statistically significant ($t = 10\ 2$, df/degrees of freedom/ $= 30$) The difference between the mean value for early pregnancy (11th–13th week of gestation) and that for the non pregnant control group, on the other hand, is not significant ($t = 1\ 69$ df $= 33$) The variances in the groups were tested by an F test and no different between the variances was found

The relation between $\log_e$ P and t (Fig 6) was calculated from the experimental observations

$y = \log_e P = 0\ 069\ t - 0\ 280$ according to (1 3)

or $P = 0\ 76\ e^{0\ 069t}$ according to (1 1)

The residual variance in y is 0 23 and the total variance in y is 0 62 The variances at the different periods of pregnancy were tested and were found *to be independent* of the period of gestation

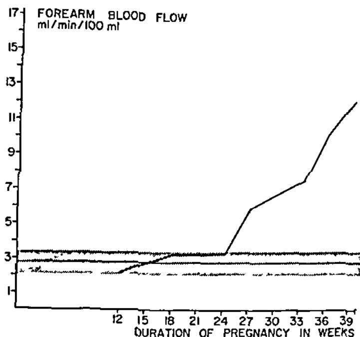


Fig 5 The mean values of blood flow in the total series (solid curve) and the 95 per cent confidence limits for the mean value of the control group (shaded area)

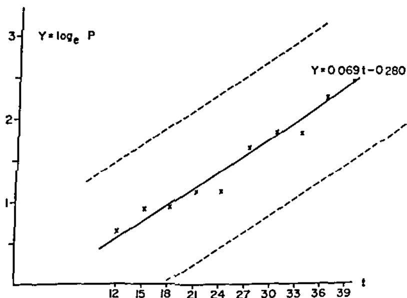


Fig 6 Blood flow as a function of the duration of pregnancy (solid line) and the 95 per cent confidence limits for a single value (dotted lines)

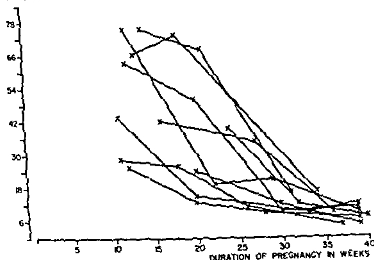


Fig 7 Peripheral vascular resistance to blood flow in relation to duration of pregnancy in 10 patients

The analysis of variance for linearity permits the conclusion that the functional relation between t and P corresponds to the assumed model [F ~ 0 63 df ≈ (8 82,)] This means that the increase of blood flow during pregnancy may follow an exponential function

The 95 per cent confidence limits for β were 0 058–0 080

Peripheral vascular resistance The data from 10 consecutive subjects can be seen in Fig 7

The general tendency to progressive dilatation of the resistance vessels is evident

As above the pregnancy was divided into three week periods for presenting the results in Table III

Table III shows the number of observations in each period, the mean values for vascular resistance, means of the logarithmic values, and the standard deviation of the logarithmic values The mean value for the non pregnant group is 40 PRU the mean logarithmic value 3 58, and the standard deviation 0 47

Table III

Duration of Pregnancy in Weeks	Number of Observations	Mean of the Observed PRU values	Mean of the $\log_e$ Values of *PRU*	Standard Deviation of the $\log_e$ Values
11–13	14	47	3 81	0 30
14–16	6	39	3 55	0 53
17–19	8	43	3 30	0 96
20–22	11	33	3 29	0 59
23–25	8	32	3 38	0 42
26–28	6	18	2 77	0 52
29–31	9	16	2 65	0 44
32–34	9	17	2 65	0 63
35–37	10	10	2 22	0 28
38–40	11	8	1 90	0 71

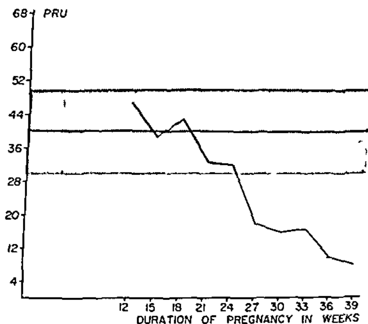


Fig 8 The mean values of peripheral vascular resistance (*solid curve*) and the 95 per cent confidence limits for the mean value of the control group (*shaded area*)

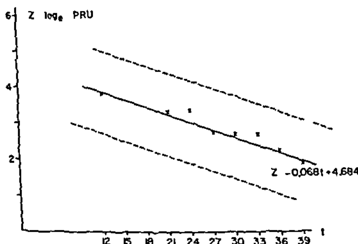


Fig 9 Peripheral vascular resistance to blood flow as a function of the duration of pregnancy (solid line) and the 95 per cent confidence limits for a single value (dotted lines)

The mean values for peripheral vascular resistance in relation to the duration of pregnancy can be seen in Fig 8 in which, in addition, the mean value and the 95 per cent confidence limits for the mean of the non pregnant group are seen

After the 25th week of gestation there is a marked decrease in resistance to blood flow which is statistically significant when compared with the value for the control group ($t=8\ 1$, $df=30$)

The difference between early pregnancy (11th–13th week) and the control group, on the other hand, is not statistically significant ($t=1\ 8$, $df=33$)

The relation between $\log_e$ PRU and t (Fig 9) was calculated from the experimental observations

$z=\log$ PRU$=-0\ 068\,t+4\ 684$ according to (1 4)

or PRU$=107\ 8\ e^{-0\ 068t}$ according to (1 2)

The residual variance in z was 0 30 and the total variance was 0 68 As regards the resting blood flow the variances were tested and an analysis of variance for testing the linearity was performed [$F=0\ 90$ $df=(8, 82)$]

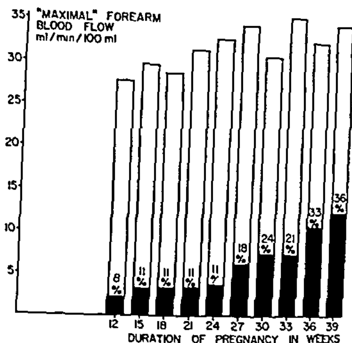


Fig 10 The mean values of maximal blood flow capacity during pregnancy and the percentage constituted by resting forearm blood flow

As before, the mathematical model could be accepted, which means that the experimental results do not contradict the assumption that the decrease in vascular resistance follows an exponential function

The 95 per cent confidence limits for δ were $-0\ 056$ — $-0\ 080$

"Maximal blood flow capacity" There was a relatively large variation between the results in different subjects and also in the same subject from one determination to another As before, the pregnancy was divided in three-week periods, and a mean value for each period was determined These results can be seen in Fig 10

As can be seen 'maximal blood flow capacity' increases during pregnancy The mean value in early pregnancy (11th–13th week) is 28 ml/min $\times$ 100 ml and at term 35 ml/min $\times$ 100 ml The difference between these two values is statistically significant ($t = 2\ 75$, $df = 28$) The mean value for the control group was found to be 27 ml/min $\times$ 100 ml There is no statistical significance

in the difference between this latter value and that of early pregnancy ($t=0.41$, $df=31$)

These results might be interpreted as indicating that the vascularity of the tissue in the forearm increases somewhat during the course of pregnancy, since functional mean arterial pressure and venous pressure remain constant

Fig 10 shows also the resting forearm blood flow (black columns) as a percentage of the simultaneously recorded maximal blood flow capacity During early pregnancy there is a local circulatory reserve in forearm blood flow which comprises approximately 90 per cent, only about 10 per cent of the blood flow being utilised at rest As pregnancy proceeds this fraction steadily increases At term about 35 per cent of the blood flow capacity is utilized under resting conditions

The forearm volume was measured on each occasion On each subject the same rubber sleeve could be used on subsequent determinations There was no change in limb volume during the course of pregnancy

Resting hand blood flow In 2 subjects hand blood flow increased from 8 5 ml/min × 100 ml in the 16th week of pregnancy up to 25 ml/min × 100 ml in the 39th week of gestation The increase of hand blood flow is of approximately the same order of magnitude as the increase in resting forearm blood flow

During thermal stimulation hand blood flow was increased by 4 to 5 times Forearm blood flow however was constant or showed a small increase

Discussion

Venous occlusion plethysmography is a generally accepted method to determine blood flow per unit time per unit tissue It is an entirely harmless procedure, one particular advantage being that it can be repeated under strictly standardized conditions A study comparing this indirect method to determine blood flow with a direct determination procedure has been published by Conrad and Green (1961) The results were the same

The blood flow through skeletal muscles and skin constitutes the main forearm blood flow The muscles make up the major

fraction of forearm volume and it has been shown that forearm blood flow is largely skeletal muscle flow (Grant and Pearson, 1938, Allen, Barcroft, and Edholm, 1946) The measurements were performed in order to study the general trends of blood flow in the extremities There is every reason to believe that the changes of blood flow in the extremities reflect the general tendency in a much larger fraction of total body mass, namely total skeletal muscles The skeletal muscles constitute approximately 40 per cent of total body mass Although the measurements have been performed on a rather restricted area the results obtained are probably representative of the circulation in a major fraction of the body

It could be argued that the increase in forearm blood flow measured in this investigation could be due to a large selective increase of skin blood flow Of the total blood flow through the hand, the greater part passes through skin Total hand blood flow therefore is largely skin blood flow (Grant and Pearson, 1938, Greenfield, 1963) Blood flow to the skin is determined by the need to maintain thermal balance (Greenfield, 1963) Simultaneous measurements of forearm and hand blood flow during thermal stimulation showed that hand blood flow was increased to radiate heat from the body whilst forearm blood flow was interfered with very little Of total forearm tissue volume only a minor part is skin Thus a very large increase in skin blood flow during pregnancy would be required to explain the increase of total forearm blood flow In accordance with the results of Abramson, Flachs, and Fierst (1943) and Burt (1950), and with those in the present study the increase in forearm blood flow could not be solely due to a selective increase in skin blood flow The findings can only be explained by a considerable increase in the blood flow through the muscles

Since the rate of blood flow is very labile it is important to standardize the experimental conditions as much as possible A few patients were disturbed during the measurements and this was associated with changes in blood flow As this lability and its cause were obvious, in some cases single observations were excluded from the material At an advanced stage of pregnancy a few women were disturbed by the recumbent position and

measurements could therefore not be performed It should be pointed out that the only reason to exclude a measurement was that standardized experimental conditions could not be achieved

In previous studies on peripheral blood flow during pregnancy the experimental conditions have not been strictly defined This fact makes a comparison with the present data difficult

It is well known that the venous pressure in the lower extremities increases towards the end of pregnancy (Mc Lennan, 1943) This may interfere with the circulation in this region On the other hand according to McLennan (1943) the venous pressure in the forearm is unchanged during pregnancy and therefore in the present study measurements were performed on the upper extremity

Abramson, Flachs, and Fierst (1943) postulated that the peripheral circulation would increase during pregnancy in conformity with the increase in cardiac output However they could not find any evidence in support of this assumption in their studies on the circulation in the lower limb In only 3 out of 11 patients, in which the forearm blood flow was measured, could an increase in blood flow be demonstrated The total number of patients and of observations on each of them was limited however, and this may explain the divergence between their findings and those presented here

Burt (1950) has reported measurements of forearm blood flow on 8 pregnant women, each of them examined once only She found an increase during pregnancy but did not differentiate between the results obtained during early and late pregnancy All observations on pregnant women were consequently compared with those from the non pregnant women

The most extensive series of measurements of this kind has been presented by Herbert Banner, and Wakim (1954, 1958) In a control group they found a mean value of $4\ 56 \pm 0\ 10$ ml/min $\times$ $\times$ 100 ml

The individual variations are surprisingly small They did not find any difference in blood flow in the control group which could be attributed to different menstrual phases An average increase of approximately 90 per cent in forearm blood flow as late as the 36th–37th week of gestation was found This increase is much

smaller than that found in the present study They also noted a decrease in blood flow during the last few weeks of pregnancy Such a decrease could not be detected in the present study

SUMMARY

1 Resting forearm blood flow and "maximal blood flow capacity" during reactive hyperæmia were determined by venous occlusion plethysmography Twenty-seven pregnant women were examined, usually four times during pregnancy, and compared with a control group of 21 non-pregnant women

2 Non pregnant women had a mean forearm blood flow of 2 8 ml/min $\times$100 ml At the 11th–13th week of gestation the mean value for resting forearm blood flow was 2 1 ml/min $\times$100 ml There was no statistical difference between these two values During pregnancy there was a gradual increase in forearm blood flow, mainly occurring during the latter half of pregnancy At term the blood flow was 12 3 ml/min $\times$100 ml The increase is statistically significant when compared with the value of the control group

3 Non-pregnant women had a peripheral vascular resistance to blood flow of 40 PRU At the 11th–13th week of gestation the mean value for peripheral resistance was 47 PRU There was no statistical difference between these two values During pregnancy there was a decrease in peripheral resistance to 8 PRU at term This decrease was statistically significant

4 Maximal blood flow capacity ' in the control group was 27 ml/min $\times$100 ml The mean value in the 11th–13th week of gestation was 28 ml/min $\times$100 ml There was no statistical difference between these two values At term the maximal blood flow capacity was 35 ml/min $\times$100 ml There are great variations between the values but the increase during pregnancy is statistically significant

5 The ratio between resting forearm blood flow and maximal blood flow capacity ' increases gradually during pregnancy

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From the First Women's Clinic (Professor Aarno Turunen), and the Renal Ward, Fourth Department of Medicine (Professor Bertel von Bonsdorff), University of Helsinki, Finland

SERUM URIC ACID IN TOXÆMIA OF PREGNANCY WITH SPECIAL REFERENCE TO THE PROGNOSIS OF THE FŒTUS

BY

BÖRJE KUHLBÄCK AND OLOF WIDHOLM

During normal pregnancy certain changes in the concentration of serum uric acid occur Previously, somewhat conflicting data have been published regarding the changes encountered in the different stages of pregnancy, but recently Steenstrup (1963) has convincingly shown that hypouricæmia is present in the first and second trimesters of a normal pregnancy, while in the third trimester the uric acid concentration in the plasma is the same as in the non-pregnant individual During parturition the uric acid concentration in the serum usually rises to hyperuricæmic values, but returns to normal by the third–fifth day of the puerperium

The results relating to serum uric acid in pregnancies accompanied by hyperemesis, toxæmia and pre-eclampsia are less clear-cut However, the majority of authors have reported that the uric acid concentration in the serum is elevated in these conditions, particularly in severe cases of toxæmia (Slemons and Bogert, 1917, Caldwell and Lyle, 1921, Killian and Sherwin, 1921, Harding and Drew, 1923, Peckham 1929, Stander and Cadden, 1934, Hayashi, 1956, Lancet and Fisher, 1956, Czaczkes *et al*, 1958, Novell and de Haan, 1958)

Aided by a grant from the Sigrid Juselius Foundation

Table I *Composition of the Series*

Group		Age yrs	Plasma creatinine mg %	Non-protein nitrogen mg
1 Controls	(72)			
	Mean	26 3	0 53	31 5
	Range	16–41	0 30–0 94	20–45
2 Hyperemesis and/or Nephrogestosis	(31)			
	Mean	25 9	0 75	32 1
	Range	17–42	0 54–1 04	25–50
3 Toxæmia	(37)			
	Mean	26 5	0 77	36 8
	Range	18–41	0 54–1 00	25–65
4 Pre Eclampsia or Eclampsia	(24)			
	Mean	29 5	0 86	35 3
	Range	19–42	0 36–1 22	25–60

The present study was undertaken in order to evaluate the serum uric acid concentration in different stages of toxæmia of pregnancy and in order to find out whether an elevation of the level at the end of pregnancy is related to complications of delivery or to birth weight and the condition of the baby at birth This is a question of major interest in Finland, in particular, where the incidence of toxæmia is high (about 10 per cent) A further stimulus was the observation that all patients with toxæmia admitted to the Renal Ward for treatment of uræmia either prior to or after delivery exhibited extremely high serum uric acid values quite out of proportion to the renal failure

Series and methods

The series consists of 92 pregnant women showing signs of toxæmia of varying degree A total of 72 normal pregnant women were used as controls (Table I) The control series also includes a few patients with slight vomiting Only toxæmic patients with normal or very slightly impaired renal function were included in the series Patients with definite signs of hepatic insufficiency were omitted The toxæmic patients were divided in three groups (groups 2–4) using the criteria recommended by the American Committee of Maternal Welfare (Werko 1948)

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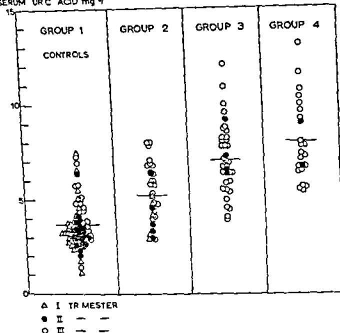


Fig 1 Distribution of serum uric acid levels in the different groups

the present series It is evident that patients with toxæmia pre-eclampsia or severe eclampsia, have a marked hyperuricæmia, but as a rule patients with a milder degree of toxæmia also exhibit elevation of the uric acid concentration in the serum It has also been shown that these patients have decreased uric acid clearance values (Chesley and Valenti 1958 Pollak and Schewitz 1963) and their urate excretion is markedly decreased (Stander and Cadden 1934 Hayashi, 1956, Czaczkes *et al* 1958) although it may be enhanced with probenecid (Czaczkes *et al* 1958) In our series there is considerable overlap between the uric acid values in the different groups Hence a single test value is not enough for determining the severity of toxæmia in a particular patient

Table II Uric Acid Concentration in the Serum in Toxæmia of Pregnancy

Trimester	Group 1 (Controls)		Group 2		Group 3		Group 4	
	Number of determinations	Serum uric acid mg %	Number of determinations	Serum uric acid mg %	Number of determinations	Serum uric acid mg %	Number of determinations	Serum uric acid mg %
1st	27	3 68	7	4 16	0	–	0	–
2nd	27	3 21	5	4 22	4	7 28	2	7 85
3rd	18	4 48	19	5 92	33	7 04	22	8 03
Mean	72	3 70	31	5 24	37	7 06	24	8 02

Furthermore, the series was divided into three groups according to duration of pregnancy, i e from the 6th–12th week, from the 13th–28th week and from the 29th–42nd week (first, second and third trimester)

Serum uric acid was determined by the uricase method of Praetorius (1953) In our laboratory the normal values for women are 2 5–5 7 mg% Values between 2 0 and 3 7 mg% are regarded as slight hypo-uricæmic

Results and discussion

The results are shown in Table II and Fig 1 The mean serum uric acid value in the control series (Group 1) is in the lower range of normal (3 7 mg%) In the first and second trimesters a slight hypo-uricæmia is observed, while the uric acid concentration is normal in the third trimester These results are entirely in agreement with those of Steenstrup (1963)

In Groups 2–4 the mean serum uric acid values are definitely elevated In the different trimesters in the toxæmia Group 3 the distribution corresponds largely to the results reported by Schewitz *et al* (1962), i e that if pre-eclampsia or eclampsia occur before the 28th week of pregnancy, the uric acid values are higher than in late pregnancy The groups being small, however, no conclusions can be drawn

These results are in good agreement with those of certain previous authors, Lancet and Fisher (1956) in particular Age (within 16–42 years), parity and diet do not influence the results (Steenstrup, 1963), and renal failure or gout, which may change the serum uric acid concentration, did not occur in

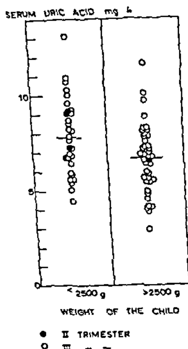


Fig 3 Relationship between serum uric acid concentration and birth weight of the baby in toxæmia of pregnancy (Groups 2–4)

markedly higher (8 0 mg%) in the mothers delivered by Cæsarean section than in those who had spontaneous deliveries (6 6 mg%) The difference is significant ($P < 0\ 02$) Furthermore, the uric acid concentration was higher (7 9 mg%) in the mothers who gave birth to premature babies (weight under 2 500 g) than in those who were delivered of babies weighing over 2 500 g (6 6 mg%) This difference al o is significant ($P < 0\ 02$) By contrast there was hardly any correlation demonstrable between the condition of the baby at birth, as judged by Apgar scores and the serum uric acid value of the mother at the end of pregnancy, but the groups in our series are too small and the differences between them are too slight to allow any definite conclusions on this point

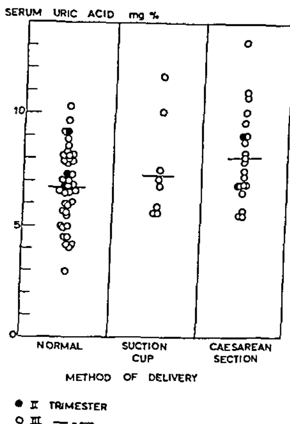


Fig 2 Relationship between serum uric acid concentration and mode of delivery in toxæmia of pregnancy (Groups 2–4)

High uric acid values in the serum did not correlate with any special sign in Groups 3–4, as the degree of œdema, hypertension or proteinuria

Mechanism of delivery and condition of the baby Czaczkes *et al* (1958) held that the serum uric acid value in eclampsia is of prognostic significance from the standpoint of the mother In the present series there was no fatal outcome In order to evaluate the possible significance of the uric acid level from the standpoint of the baby, we collected the data relating to mode of delivery, and birth weight and condition of the baby at birth, in 69 cases in Groups 2–4 The results are shown in Figs 2–3

As appears from the figures, the serum uric acid level was

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Five infants were stillborn The mean of the serum uric acid concentration in the mothers of these infants was 7 6 mg%

On the basis of the present results it seems to be important to determine the uric acid concentration in the serum in all cases of suspected or established toxæmia of pregnancy, in order to evaluate the degree of the toxæmia and to assess the optimum time of delivery

SUMMARY

The uric acid concentration in the serum was studied in 72 normal pregnant women and in 92 pregnant women with varying degrees of toxæmia In the toxæmic cases a marked elevation of the serum uric acid level was observed, and the severer the toxæmia, the higher was the uric acid concentration There was considerable overlap between the uric acid values in the different groups, however Hence, this test can hardly be regarded as having a diagnostic value In none of the present cases was the outcome fatal to the mother, but in five cases it was fatal to the baby

The toxæmic mothers delivered by Cæsarean section showed significantly higher serum uric acid values (8 0 mg%) than those who had spontaneous deliveries (6 6 mg%) Furthermore, the uric acid concentration was significantly higher (7 9 mg%) in the toxæmic mothers who gave birth to premature babies (under 2500 g) than in those who were delivered of babies weighing over 2500 g (6 6 mg%) From the standpoint of evaluating the degree of toxæmia and prognosticating the course of the delivery, the importance of determining the serum uric acid concentration in all cases of suspected or established toxæmia of pregnancy is emphasized

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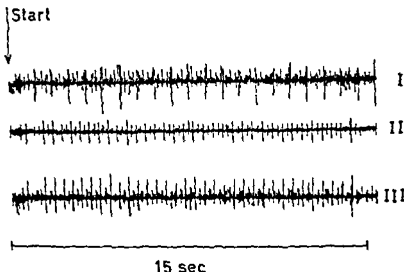


Fig 1 Three bands of fœtal phonocardiograms (*System* Elema Stockholm) Arrow indicates start of auscultation of fœtal heart rate for the following 15 seconds Paper speed 10 mm per second—According to phonocardiographic recording 152 beats per minute Corresponding figure for simultaneous auscultation 148 beats per minute

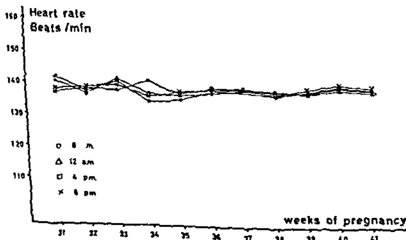


Fig 2 Mean values of fœtal heart rate at four different times of the day and calculated per gestational week. Ordinate beats per minute Abscissa weeks of pregnancy

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FŒTAL HEART RATE DURING THE THIRD TRIMESTER OF TOXÆMIC PREGNANCY AND IN FŒTAL DISTRESS BEFORE THE ONSET OF LABOUR

BY

INGEMAR JOELSSON AND BJÖRN WESTIN

Impaired fœto-maternal exchange of blood gases and nutritional substances across the placental barrier constitutes the condition known as placental dysfunction Such dysfunction often causes fœtal distress or fœtal death in utero and is most often encountered in association with *toxæmia* (Jayle and Crepy, 1955, Furuhjelm, 1962 and references therein, Snoeck and Schwers, 1963), *diabetes* (Hagbard, 1956, Snoeck and Schwers, 1963), or *prolonged pregnancy* (Runge, 1939, Lindgren *et al*, 1958, and references therein)

Before onset of labour mild intrauterine asphyxia may lead to fœtal tachycardia (Reynolds, 1960) Thus, regular recording of fœtal heart rate by means of auscultation at frequent intervals could be a simple method to detect fœtal distress caused by impaired fœto-maternal exchange of blood gases

The intention of the present investigation is primarily to present mean values and confidence limits for fœtal heart rates in toxæmic patients during the third trimester before onset of labour and secondly to point out the possibility of using heart rate determination by auscultation as an additional sign in the diagnosis of fœtal distress

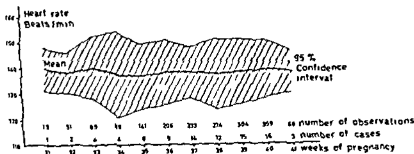


Fig 4 Mean values and 95 per cent confidence limits of fœtal heart rate during the 31st to 41st week of pregnancy in 36 toxæmic patients Number of cases and number of observations for each week of pregnancy are indicated in the diagram Ordinate beats per minute Abscissa weeks of pregnancy

potassium chloride 0 5–2 0 gm and, when hypertension did not respond to this treatment, hydralazines 0 05–0 45 gm daily In the dosages given and administered these drugs did not significantly alter fœtal heart rate

Toxæmic control series —This series comprised 36 patients between 19 and 41 years of age Twenty six patients were primigravidæ and 10 were multigravidæ In all of these patients only small fluctuations in fœtal heart rate were observed throughout the period of observation, which in general lasted for 2–3 weeks and occasionally for as long as 6 weeks —There were 4 patients with toxæmia Grade I 27 patients Grade II and 5 patients Grade III

Fœtal distress series —This series comprised only 4 cases obtained during the same period of observation The fœtal heart rate having been at a normal level (mean ± 2 s d), was followed by tachycardia (>mean + 4 s d) of a degree not encountered in the control series There were 3 patients with toxæmia Grade III (including one diabetic patient) and one patient with toxæmia Grade II

Determination of Fœtal heart rate —Fœtal heart rate was determined by auscultation with the patient resting in the supine position Auscultation of heart sounds was performed during one, two or occasionally four consecutive 15 second periods The same

s d = standard deviation

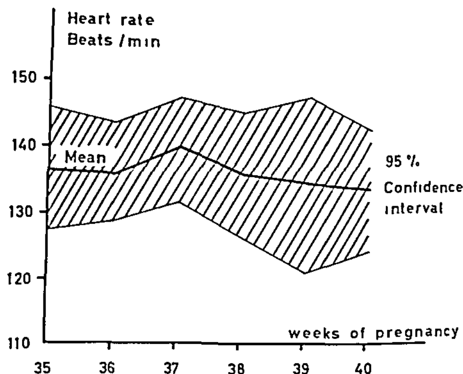


Fig 3 Mean values and 95 per cent confidence limits of fœtal heart rate during 35th through 40th week of pregnancy in a patient with toxemia Grade II Each mean is calculated from 28 single observations Ordinate beats per minute Abscissa weeks of pregnancy

Material and Method

The material was collected between February 1961 and April 1964 and comprised patients admitted to hospital because of toxæmia in the third trimester Classification of toxemias was as follows *Grade I* One or two of the following signs Clinically evident œdema, proteinuria or arterial hypertension (140–160/90–110 mm Hg) *Grade II* All of the three following signs Clinically evident œdema, proteinuria, arterial hypertension (140–160/90–110 mm Hg) *Grade III* All signs listed for Grade II but systolic blood pressure exceeding 160 and diastolic pressure above 110 mm Hg

Grade II and III patients were confined to bed while Grade I patients were permitted some physical exertion within the ward —Therapeutic drugs administered were chlorthiazide 0 5–1 0 gm,

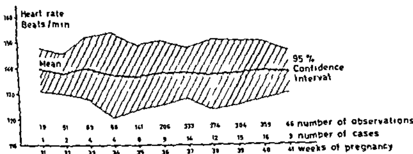


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Toxæmic control series—This series comprised 36 patients between 19 and 44 years of age Twenty six patients were primigravidæ and 10 were multigravidæ In all of these patients only small fluctuations in fœtal heart rate were observed throughout the period of observation, which in general lasted for 2–3 weeks and occasionally for as long as 6 weeks—There were 4 patients with toxæmia Grade I, 27 patients Grade II and 5 patients Grade III

Fœtal distress series—This series comprised only 4 cases obtained during the same period of observation The fœtal heart rate having been at a normal level (mean ±2 s d) was followed by tachycardia (>mean +4 s d) of a degree not encountered in the control series There were 3 patients with toxæmia Grade III (including one diabetic patient) and one patient with toxæmia Grade II

Determination of Fœtal heart rate—Fœtal heart rate was determined by auscultation with the patient resting in the supine position Auscultation of heart sounds was performed during one, two or occasionally four consecutive 15 second periods The same

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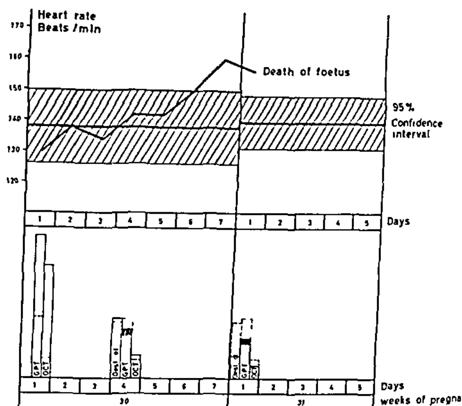


Fig 5 Fœtal distress series Case 1, I para, 33 years, toxæmia Grade III A slow rise in fœtal heart rate followed by intrauterine fœtal death (weight 1120 gm) is illustrated Mean values and 95 per cent confidence limits of fœtal heart rate for the 31st week are given (see Fig 4) Because of lack of material, mean and confidence limits for the 30th week of pregnancy were calculated from the whole series Transaminase activities (GPT, OCT) and œstriol excretion in urine are also given Upper normal limits for transaminase activities (Normann Teger Nilsson, and Westin, 1960), and lower normal limit for œstriol excretion (Furuhjelm, 1962), are indicated by dotted lines within the columns Ordinate beats per minute Abscissa days and weeks of pregnancy

midwives performed the auscultation every 4th hour from 8 a m until and including 8 p m throughout the period of investigation

The error in the subjective evaluation of fœtal heart rate was determined by simultaneous and indepent recording of fœtal heart rate by phonocardiography and auscultation during 15 second periods (Fig 1) Thirty-five such double determinations were performed At a fœtal heart rate of 136 per minute the error in a

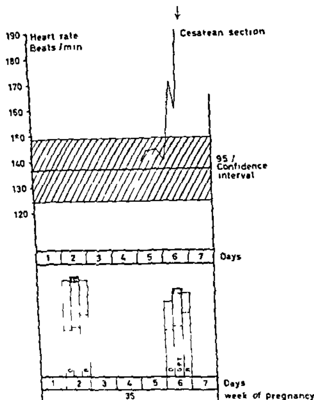


Fig 6 Fœtal distress series Case 2 II para 37 years toxæmia Grade III Infant weight 2090 gm A sharp rise in fœtal heart rate is illustrated Infant delivered by Cæsarean section was covered with meconium and was asphyxiated Mean values and 95 per cent confidence limits of fœtal heart rate for the 35th week of pregnancy are given (see Fig 4) Transaminase activity (GPT) as well as Bilirubin concentration in the blood and œstriol excretion in the urine are also given and their normal values indicated by dotted lines (see Fig 5 for references) Ordinate beats per minute Abscissa days and week of pregnancy

single subjective evaluation was 3 7 per cent. The corresponding figure at a fœtal heart rate of 156 per minute was 3 2 per cent The auscultation method for evaluating fœtal heart rate was thus accurate enough for statistical analysis of the material In the statistical analysis single observations of fœtal heart rate at maternal body temperature above 37 5°C were discarded

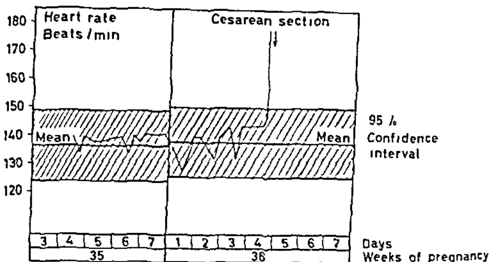


Fig 7 Fœtal distress series Case 3 I para, 23 years, toxæmia Grade III and diabetes mellitus Infant weight 2650 gm Figure illustrates a sudden and marked rise in fœtal heart rate—a fairly tight true knot in the umbilical cord was present and the infant was slightly asphyxiated after delivery by Cæsarean section Mean values and 95 per cent confidence limits of fœtal heart rate during the 35th and 36th week of pregnancy are given (see Fig 4) Ordinate beats per minute Abscissa days and weeks of pregnancy

Results

Toxæmic control series—No significant changes in fœtal heart rate occurred from day to day within any particular week from the 31st to and including the 41st week of pregnancy The observations of fœtal heart rate are therefore presented as mean values for each week of pregnancy Fig 2 illustrates the mean values of fœtal heart rate at four different times of day for each week of observation The four curves in the diagram are nearly identical, with no significant difference between any points of the curves The statistical material may thus be presented as weekly mean values of fœtal heart rate and independent of time of observation An example of a single patient is shown in Fig 3 and the whole material in Fig 4, where weekly means with 95 per cent confidence limits are given

No significant difference in fœtal heart rate was found either between primi- and multigravidæ or between patients with various grades of toxæmia Even if in a larger series minor differ-

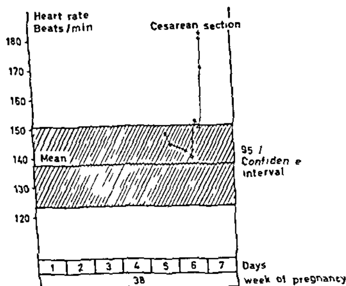


Fig 8 Fœtal d stress series Case 4 III para 40 years toxæmia Grade II Infant weight 3630 gm Figure illustrates a sharp and marked rise of fœtal heart rate Mean values and 95 per cent confidence limits for the particular week of pregnancy are given Infant was delivered by Cæsarean section in good condition. Ordinate beats per minute Abscissa days and week of pregnancy

ences could be shown to exist this is not of any practical importance in the evaluation of heart rate in fœtal distress since confidence limits will hardly be influenced The fœtal heart rate did not even differ significantly when the rate in the 31st week was compared with that in the 41st The mean fœtal heart rate during the 31st to 41st week of pregnancy was 138 ± 12 beats per minute (95 per cent confidence limits) Before onset of labour no abnormal fœtal heart rates (> ± 2 s d.) were recorded Thirty patients were delivered spontaneously one infant was slightly asphyxiated and recovered after cutaneous stimulation Six patients were delivered by Cæsarean section after onset of labour because of imminent asphyxia Two infants were slightly asphyxiated one infant recovered unaided and the other after stimulation In the cases where the infants were asphyxiated at birth no recordings of fœtal heart rate immediately prior to labour

had been performed because at that time the patients were dismissed from the hospital

Fœtal distress series—*Case 1*, I para, 33 years, toxæmia Grade III, 30th week of pregnancy is illustrated in Fig 5 A slow rise in fœtal heart rate above the upper confidence limit is seen and this was followed by fœtal death The rise in heart rate was preceded by high transaminase activity falling within the normal range at the time of onset of fœtal tachycardia (For normal range values, see Normann, Teger Nilsson and Westin, 1960) Œstriol excretion in urine was normal when the fœtal heart rate started to increase and was at a subnormal level at the time of death of the fœtus Unfortunately, however, this low value was not received until after the death of the fœtus This patient happened to be our first case of fœtal heart rate recording and because we had not any control cases we were not fully aware of the dangers of this moderate fœtal tachycardia In addition, the fœtus was estimated to weigh well below 1500 gm with a calculated mortality risk of more than 75 per cent Under these circumstances it was not felt justified to perform a Cæsarean section on this patient, with severe toxæmia and a fragile fœtus The fœtus was delivered spontaneously 9 days after its death was recorded It was a macerated premature weighing 1120 gm The placenta showed numerous small disseminated infarcts and one large circumscribed infarct measuring about 3 cm in diameter

Case 2, II para, 37 years, toxæmia Grade III, 35th week of pregnancy is illustrated in Fig 6 In this case the fœtal heart rate showed a marked rise above the upper confidence limit Between 11 a m and 5 p m the fœtal heart rate was closely observed and varied between 160 and 170 beats per minute One hour later the rate had increased to between 190 and 200 beats per minute Cæsarean section was performed immediately and the infant was covered with meconium and moderately asphyxiated It weighed 2090 gm and recovered after resuscitation The placenta was normal on macroscopical examination Transaminase activities (GOT, GPT and OCT) were high 9 days before Cæsarean section OCT returned to normal within 4 days but GOT and GPT remained high until the episode of fœtal tachycardia A second rise in GOT activity occurred on the day of Cæsarean section Urinary œstriol excretion was normal both 8 days before delivery (13 9 mg/24 hrs) and on the day of Cæsarean section (11 8 mg/24 hrs)

Case 3 I para, 23 years, toxæmia Grade III and diabetes mellitus, 36th week of pregnancy On day 4 in this week a sudden and marked rise in fœtal heart rate was observed (Fig 7) This fœtal tachycardia formed the indication for immediate delivery of the fœtus because of two severe maternal diseases known to increase the risk of intrauterine fœtal death At Cæsarean section a fairly tight true knot in the umbilical cord was found and the infant was slightly asphyxiated The infant weighed 2650 gm and recovered unaided Both one week before and on the day of Cæsarean section transaminase activities and œstriol excretion in the urine (12 4 mg/24 hrs) were normal The placenta was normal on histological examination

Case 4 III para 40 years toxæmia Grade II 38th week of pregnancy is illustrated in Fig 8 Several observations of normal fœtal heart rate were followed by a sharp and marked rise above the upper confidence limit. This tachycardia was observed for one hour and then regarded as an indication for Cæsarean section The infant weighed 3630 gm and was delivered in good condition The placenta exhibited arteriosclerotic changes and marginal infarction Transaminase activities (GOT GPT and OCT) were normal on the day of Cæsarean section.

Discussion

In the evaluation of the present results discussion will first deal with the accuracy of the auscultation method and the effect of emotional stress and body temperature on fœtal heart rate

The analysis of the toxæmic control series revealed a surprisingly small variation in fœtal heart rate from the 31st to and including the 41st week of pregnancy not only in the same subject but also between different subjects Confidence limits in the control series given with 95 per cent accuracy have a range of only ± 9 per cent of the mean value of fœtal heart rates in the whole series This makes the simple and rapid clinical method of evaluating fœtal heart rate extremely suitable for determination of expected changes in rate provided the method is fairly accurate Subjective evaluation of fœtal heart rate compared with simultaneous phonocardiographic records has shown the method error to be extremely small, at least within the ranges tested This was not unexpected since a similar high degree of accuracy has been obtained between two independent subjective observers of fœtal heart rate (Beard, 1962) Increases in both adrenaline and noradrenaline are known to occur in adults as the results of emotion (Elmadjian *et al* 1957) and these substances may also influence the heart rate of the human fœtus (Beard, 1962) Attempts were made to reduce emotional stress by using the same observers (midwives) of fœtal heart rate throughout the investigation

A slight rise in body temperature (0 3°–0 5°C) was present when the afternoon auscultations were performed (at 4 p m) However this slight rise did not significantly alter the heart rate in comparison with the morning observations (at 8 a m) As patients within toxæmia Grades II and III were advised rest in

bed and the few patients in Grade I only were allowed slight excercise within the ward, physical exertion was estimated to be slight Yet it is possible that the effect of elevated body temperature upon metabolic rate and thus fœtal heart rate might have been counteracted by fœtal bradycardia induced by muscular exercise (Morris *et al*, 1956)

It is puzzling why no significant difference in fœtal heart rate was found between cases of mild and severe toxemia There appear to be at least two possible mechanisms by means of which the fœtus may increase its oxygenation without tachycardia, provided intrauterine asphyxia progresses very slowly One of these mechanisms would be increased fœtal placental blood flow at unchanged heart rate through progressive increase in cardiac stroke volume Another mechanism which might operate at unchanged heart rate would be increased oxygen binding capacity of the fœtal blood (total hæmoglobin content) elicited by hypoxic stimulation of the hæmatopoetic system Both of these mechanisms could be assumed to operate within a limited range of hypoxia As hypoxia gradually deepens this limit might be exceeded and another compensatory mechanism is set at work in the form of a progressive change in heart rate as observed in the present fœtal distress series

In four patients fœtal tachycardia was observed of a degree never present in the control series (4–10 s d above mean values of heart rate of control series) This raises the question of why the fœtal heart in some cases of toxemic pregnancy responds *with tachycardia rather than bradycardia?*

During labour dips in fœtal heart rate occur after the peak of each uterine contraction Uterine ischæmia or increased intracranial pressure causing vagal stimulation of the heart are possible explanations (Hon *et al*, 1961, Caldeyro Barcia *et al*, 1963, Mendez-Bauer *et al*, 1963)

However, tachycardia has also been reported to occur during labour It has been suggested that a mild degree of tachycardia may be an earlier sign of fœtal distress than bradycardia (Brady and James, 1962)

In toxæmic pregnancies placental degenerative changes are frequently present and may be accompanied by a precipitous fall

in œstriol excretion in urine In these cases placental dysfunction may be so extensive as to cause fœtal death in utero (Snoeck and Schwers, 1963) It seems reasonable to assume that the fœtus in such cases has experienced a more or less prolonged period of asphyxia before death occurs

In the *absence* of uterine contractions and engagement of the fœtal head the effect of hypoxia on the fœtal heart may be expected, at least in the initial stages, to be an increase in fœtal heart rate The response of the fœtal heart may probably be mediated through hypoxæmia induced release of adrenaline or similar substances (Dornhorst and Young, 1952, Reynolds, 1960, Beard, 1962) Within a reasonable range of heart rate, cardiac stroke volume can be assumed to be approximately constant An increase in fœtal heart rate will thus be a measure of a corresponding rise of cardiac minute volume

In humans normal fœtal, placental vessels respond to hypoxæmia with decreased vascular resistance (Nyberg and Westin, 1957) On the assumption that this response also will occur in toxæmic pregnancy with placental dysfunction the increase in fœtal heart rate may be interpreted as an attempt by the fœtus to maintain adequate oxygenation

The present discussion fits well with results obtained from animal experiments From these it has been suggested that mild but prolonged asphyxia may result in fœtal sympathetic response with secretion of endogenous adrenaline and fœtal tachycardia Acute and severe asphyxia produces bradycardia (Reynolds, 1960 Brady and James 1962) presumably by direct depression of the myocardium by asphyxial changes

A further testing of this hypothesis on fœtal tachycardia would be to administer oxygen for a short period of time to toxæmic mothers who show significant increase in fœtal heart rate In the presence of moderate placental dysfunction the fœtal heart rate might then be expected to fall into normal range, while this might not occur when placental dysfunction is severe Additional information about the effect of asphyxia on fœtal heart rate might be obtained by inducing slowly progressive but mild hypoxia in normal and toxæmic pregnancy before the onset of labour

Case 1 in the fœtal distress series appears to indicate that

even a moderate degree of tachycardia (4 s d above mean heart rate of control series) is of significance and if allowed to persist will lead to fœtal death If delivery is instituted upon first signs of fœtal tachycardia the chances of obtaining a living infant are good In these cases we do not always find microscopical placental signs corresponding to the recorded tachycardia The explanation may be that vasospasm precedes microscopical placental changes and may have the same functional effect on the fœtus as these, which must apparently reach a certain magnitude before a drop will be noted in œstriol excretion in the urine

It appears justified to recommend frequent recording of fœtal heart rate in all women during the third trimester where intrauterine asphyxia can be suspected The results of the present study imply that this would be a valuable additional aid in the prevention of fœtal death in utero

SUMMARY

Fœtal heart rate was observed by means of auscultation during the third trimester of toxæmic pregnancy The error in the subjective evaluation of heart rate was investigated and found to be small Fœtal heart rate was fairly steady from the 31st to 41st week of pregnancy and independent of the period of gestation and the time of day during which the observations were performed The average fœtal heart rate in 36 toxæmic patients for the period of investigation was 138 ± 12 beats per minute (95 per cent confidence limits)

Using these confidence limits 4 additional toxæmic patients showed abnormal fœtal heart rates All of them exhibited tachycardia These cases are described in detail and possible causes of fœtal tachycardia are discussed

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CONSTANCY OF INDIVIDUAL MENSTRUAL BLOOD LOSS

BY

LEIF HALLBERG AND LENNART NILSSON

The loss of iron during menstruation is one of the main factors influencing the iron balance in women However, the knowledge of the magnitude of the menstrual blood loss and its variation is fairly limited In investigations on healthy women the average blood loss per menstrual period was of the magnitude 40—50 ml (Barer and Fowler, 1936, Arens, 1945) There was, however, a great range in the volume of blood loss in different women — from about 5 to 180 ml

The great variation observed in menstrual blood loss may be due to a variation in the individual from one menstrual period to another or to a variation between individuals Knowledge of the source of variation is important when evaluating the effect of menstrual blood loss on the iron balance in women So far, no systematic studies have been published on the variation of the menstrual blood loss in the individual woman or between women in general

In those studies where successive periods have been analysed, the variation between periods was considered to be marked (Arens, 1945, Schlaphoff and Johnston, 1949, Baldwin, Whalley and Pritchard, 1961) or to be marked in some individuals (Barer and Fowler, 1936, Millis, 1951) In one study only (Leverton and Roberts 1937) the variation was considered to be slight In the latter investigation the series comprised 4 healthy college women, each studied for 3 to 6 periods

In a previous paper (Hallberg and Nilsson, 1964) where

Table I *Composition of material*

Subject	Age	Height (cm)	Weight (kg)	Hæmoglobin gm/100 ml
1	23	169	58	12 5
2	22	168	61	12 9
3	21	161	53	13 0
4	23	170	57	13 5
5	22	167	56	13 4
6	22	165	59	13 2
7	22	167	60	12 7
8	21	164	58	13 7
9	21	174	63	13 4
10	23	159	51	13 7
11	22	167	54	14 5
12	22	168	60	14 5

two subjects were studied for twelve consecutive menstrual periods the variation observed between periods was very small, indicating that the main variation is related to differences between individuals

Material and Methods

Twelve healthy probationer nurses between 21 and 23 years old were studied Some physical data are given in Table I

The menstrual blood loss was determined according to a method previously described (Hallberg and Nilsson, 1964) The method is based on the simultaneous use of tampons and towels for the collection of menstrual blood and an extraction of these with 5 % sodium hydroxide thus also converting the hæmoglobin to alkaline hæmatin The latter is determined spectrophotometrically The method is very simple and gives accurate results as shown in a series of experiments

Detailed instructions were given to each subject before starting the study and after each period an interrogation was made as to the completeness of the collection All subjects were aware of the purpose of the study and of the importance of careful collection The amount of hæmoglobin lost was determined and the blood loss was calculated from the hæmoglobin concentration of a venous blood sample, using the cyanmethæmoglobin method

Table II *Menstrual losses of iron (milligrams) (12 periods in 12 subjects)*

Subject	MENSTRUAL PERIOD												Mean Value and Standard error of Mean
	1	2	3	4	5	6	7	8	9	10	11	12	
1	14 4	8 4	9 4	9 7	14 7	10 4	9 0	9 0	8 4	10 0	13 4	7 7	10 4 ± 0 7
2	13 4	21 7	14 4	26 1	13 7	13 7	13 4	16 7	12 4	9 0	8 0	15 2	14 8 ± 1 4
3	4 5	4 0	4 0	4 0	3 7	7 3	4 0	2 3	3 7	4 0	3 3	3 7	4 0 ± 0 3
4	22 0	7 7	9 4	5 3	10 4	7 3	8 7	14 7	9 0	11 7	9 4	8 0	10 3 ± 1 2
5	20 4	26 4	29 7	14 7	33 1	27 7	18 0	28 4	34 4	21 0	22 0	35 4	25 9 ± 1 9
6	31 1	24 7	23 0	21 7	18 7	32 4	18 4	22 7	21 4	24 0	19 7	28 7	23 9 ± 1 3
7	10 1	8 4	5 7	7 0	4 3	7 0	5 7	4 7	6 0	5 0	6 8	8 4	6 6 ± 0 5
8	3 6	3 7	5 0	8 7	6 0	4 3	5 3	6 7	4 3	5 7	3 7	6 3	5 3 ± 0 4
9	16 4	16 4	17 0	13 7	13 0	22 4	17 7	14 4	10 7	21 4	14 4	36 7	17 9 ± 2 0
10	3 7	4 3	5 0	4 3	4 7	4 0	3 0	5 0	7 0	4 3	3 7	4 7	4 5 ± 0 3
11	13 0	10 0	12 7	13 4	14 0	8 0	7 7	12 0	16 0	11 0	19 7	11 4	12 4 ± 1 0
12	18 0	12 4	19 4	20 4	22 7	20 0	15 4	20 7	17 4	23 0	17 7	26 7	19 5 ± 1 1

Table III *Menstrual losses of iron Analysis of variance*

Variance due to	Degrees of Freedom	Variance
1 Individuals	11	679 1[1]
2 Periods	11	23 9[2]
3 Individuals × periods	121	15 6

[1] Highly significant $P < 0.001$ (1 compared with 3)
[2] Not significant $P > 0.1$ (2 compared with 3)

However, the amount of blood loss is not identical with the menstrual volume which in normal subjects is about 60 per cent greater This is confirmed by weighing of towels and tampons and is due to the presence of mucus and other debris

The amount of iron lost was calculated from the hæmoglobin loss assuming the iron content of hæmoglobin to be 0 338 per cent

Results

The losses of iron for each period and each subject are given in Table II An analysis of variance showed that the variation was mainly related to differences between individuals The variation between periods was not significantly different from the rest variance (individuals × periods) The essential results of the analysis of variance are shown in Table III

The average loss of iron per period in this material was 13 0 mg The standard deviation between individuals was 7 4 mg and between periods in individuals 0 8 mg

The calculated menstrual blood losses for each period and each subject are given in Table IV An analysis of variance of these data also showed that only the variation between individuals was significantly different from the rest variance The mean menstrual blood loss was 28 ml the standard deviation between individuals 15 3 ml and in individuals between periods 1 9 ml

The marked variation between individuals as compared to the variation between periods is evident from figure 1 where the mean loss of blood in every subject is graphed together with the standard error of the means

Table IV *Menstrual losses of blood (millilitre) (12 periods in 12 subjects)*

Subject	MENSTRUAL PERIOD 1	2	3	4	5	6	7	8	9	10	11	12	Mean Value and Standard Error of Mean
1	32.3	17.9	21.4	23.5	35.5	24.5	21.5	21.9	20.2	24.3	32.3	18.7	24.5 ± 1.7
2	31.2	48.4	34.4	61.2	32.0	32.1	31.1	38.4	28.4	20.6	18.9	37.6	34.5 ± 3.3
3	10.0	8.4	8.6	9.0	8.8	16.3	9.3	5.5	8.7	8.9	7.8	8.1	9.1 ± 0.7
4	45.2	15.8	20.2	11.5	23.3	16.3	19.1	32.4	19.8	25.9	20.6	17.5	22.3 ± 2.6
5	44.5	54.2	64.0	31.9	71.2	59.9	38.8	61.3	74.3	45.4	47.7	76.6	55.8 ± 4.2
6	61.9	49.1	46.3	41.3	35.5	62.1	35.0	43.0	40.8	45.8	37.3	54.7	46.1 ± 2.7
7	23.0	18.3	12.8	16.3	10.5	16.6	13.4	10.9	14.3	11.7	16.1	19.7	15.3 ± 1.1
8	10.8	7.5	10.9	18.9	12.8	9.2	11.9	14.7	9.5	12.7	7.9	13.6	11.7 ± 0.9
9	35.2	34.6	38.7	32.9	30.9	53.3	41.9	34.2	26.1	50.8	34.0	87.1	41.6 ± 4.7
10	7.5	8.7	10.9	9.2	9.9	8.7	6.4	11.0	15.1	9.2	8.3	10.1	9.6 ± 0.6
11	27.5	20.4	26.1	27.3	29.0	16.5	15.9	25.1	32.9	22.9	40.4	23.2	25.6 ± 2.0
12	35.9	24.8	42.5	41.7	46.4	40.9	31.0	42.1	35.5	46.7	35.8	54.5	39.8 ± 2.3

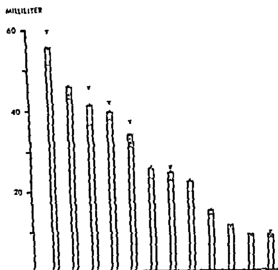


Fig 1 Menstrual blood loss in 12 subjects Mean values of 12 periods and standard error of means

Discussion

In this study the finding that the main variation in the volume of the menstrual blood loss is due to a variation between individuals is important for an understanding of the pathogenesis of iron deficiency in women Preliminary studies performed by us indicate that there is no significant difference in the magnitude of the menstrual blood loss in different age groups up to the menopause These findings together with the observed individual constancy for one whole year in the present study, would indicate that in a normal woman the menstrual loss of iron observed on one or more occasions is a fairly good measure of the average menstrual loss of iron from the menarche to the menopause

The magnitude of the iron stores must be determined by the average iron balance and time The present material was very homogenous with respect to age and body weight The food intake was fairly similar both with respect to amount and composition as judged approximately by dietary history It may thus be expected that the average iron balance and also the magnitude of the iron stores was greatly influenced by the menstrual losses of iron

An assessment of body iron stores from bone marrow examinations is greatly facilitated by simultaneous determinations of non-hæm iron and DNA, which is used as a reference (Weinfeld, 1964) In three subjects (5, 8, and 12) such studies were made In these women in their early twenties it may be expected that the iron stores are small as the iron requirements have been very great during the preceding decade During this period iron has been needed not only to cover the ordinary losses but also to satisfy the demands of growth Usually only traces of non hæm iron are observed in bone marrow smears from women of this age In two of the three subjects (5 and 12) with average menstrual losses of iron of 25 9 and 19 5 mg per period, the bone marrow nonhæm iron was 4 6 and 4 3 mg per milligram DNA respectively These concentrations indicate deficient iron stores as judged from studies of subjects with iron deficiency who had values of the order of 5 mg iron per milligram DNA (Weinfeld, 1964) However, in the third subject (8), who had a very small average loss of menstrual iron—5 3 mg per period—the nonhæm iron concentration was 7 0 mg per milligram DNA [1]

To be able to discuss the influence of the menstrual blood loss on the magnitude of the iron stores it is of course necessary to make more extensive studies in various age groups The present data is included in this paper mainly to exemplify the kind of reasoning, which it is possible to apply on the basis of the present finding of the fairly constant menstrual losses of iron

The average menstrual blood loss in this series was of about the same magnitude as reported by others In previous studies where successive periods were analysed the variation was usually considered to be great However, by analysing statistically the most extensive previous study of successive periods (Millis, 1961) we found that in that series also the variation was mainly related to interindividual differences

Knowledge of the normal variation of menstrual blood loss within individuals is of great importance, not only when evaluating iron balance in women but also when interpreting the results of

[1] The determinations of non hæm iron were kindly made by Dr Alexander Weinfeld

studies on *e g* the effect of drugs or gynæcological operations on the menstrual blood loss

This knowledge is also important in daily clinical practice It is a well known fact that it is very difficult to evaluate the magnitude of the menstrual blood loss from the subjects' own statement As a single determination of the menstrual blood loss fairly well characterises the average blood loss, it is possible to confirm or reject a diagnosis of menorrhagia from a study of one or two periods We have found this fact to be of great value in gynæcological practice as well as in the investigation of subjects with unexplained iron deficiency anæmia

SUMMARY

The menstrual blood loss was determined in twelve subjects for twelve consecutive periods An analysis of variance showed that there was a great variation in menstrual blood loss between the subjects but that the variation in the individual subject was not statistically significant

This fact has great importance when evaluating the effect of the menstrual blood loss on iron balance in women Moreover, this observation increases the practical value of single determinations of the menstrual blood loss in gynæcological and medical practice

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INTRACAVITARY CIRCULATION OF AQUEOUS MATERIAL IN THE HUMAN VAGINA[1]

BY

ERIK ODEBLAD

Vaginal discharge is one of the most common and most complex symptoms encountered in clinical gynæcology The mechanisms behind the occurrence of this symptom are known only to a small extent in spite of decades of clinical and experimental research The question will here be investigated from new aspects, with special emphasis laid on the production and path ways of the liquid phases of the contents of the vaginal cavity

It is well known that the cervix uteri secretes certain amounts of mucoid substances which contain over 90 per cent water There is also a continuous exfoliation of watercontaining cells from the vaginal epithelium In spite of these contributions of aqueous material into the vaginal lumen, the normal vaginal discharge is usually very small It was therefore suspected that mechanisms might be present causing reabsorption of water from the vagina Various aspects of this question will be investigated in this paper

The rates of inflow to the vaginal cavity and outflow from the vagina were measured quantitatively and the degree of reabsorption is calculated as the difference between these two opposite processes Possible sites of water reabsorption from the vagina were investigated and will be discussed Evidence obtained

[1] Supported by a grant from the Swedish Medical Research Council project no T 253

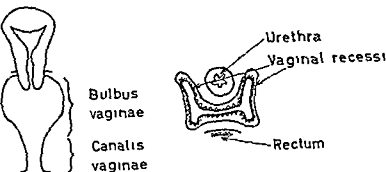


Fig 1 Left The anatomical relations showing schematically the upper dilated bulbus vaginæ and the lower narrow canalis vaginæ (frontal view) Right Cross section of the vaginal canal showing the vaginal recessi (the pockets of Shaw) and their topographical relations to the urethra

with nuclear magnetic resonance will be presented, disclosing the probable location of the reabsorption Both normal and pathological conditions are included in this study

Some remarks on vaginal anatomy and biochemistry

Before the methods and results are described the anatomy and biochemistry of the vagina will be summarized Regarded as a tubular organ the vagina shows considerable anatomic differences between the lower and upper parts The upper part of the vagina is usually dilated to a sac here called the bulbus vaginæ (BU) Fig 1 *In vivo* this sac is flat with a diameter varying from 5 to 9 cm for different individuals The lower part of the vagina on the other hand is not so wide hardly more than 4–5 cm The cross section of the lower part of the vagina is H shaped The limbs of the H extend posteriorly and more markedly anteriorly On either side of the urethra two pockets are thus formed This lower part of the vagina is here called canalis vaginæ (CA) and the anterior pockets known in the literature as the folds of Shaw (Krantz 1959) are called the vaginal recessi (Re) These pockets are of special interest here as strong evidence will be presented that they may be an important location for reabsorption of intravaginal water

The normal contents of the human vagina are (1) Exfoliated

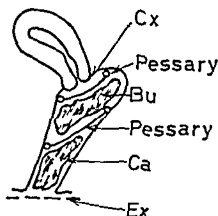


Fig 2 Approximate locations of diaphragms and interposed absorbent material in bulbus (Bu) and canalis (Ca) vaginæ External absorbent layer (Ex) is also indicated.

cells containing intracellular water, electrolytes, glycogen and other organic compounds (2) Extracellular fluid resembling a transudate, containing water, electrolytes, proteins, amino acids and other compounds (3) Mucus, mainly deriving from the cervix, a gel with varying composition At ovulation the proportion of water is very high It also contains electrolytes and polysaccharides (4) Lactobacilli, degrading glycogen and enzymes capable of depolymerizing the cervical mucus and liquefying other mucous substances normally present in the vagina (5) During menstruation and, sometimes, at ovulation there is also blood and its decomposition products Water, electrolytes and other low-molecular substances appear specially liable to be reabsorbed by the vaginal mucosa

Clinical material

The material underlying this study comprises 19 volunteers, 12 healthy women and 7 women suffering from non-specific vaginal inflammation of over five years duration All these women were subjected to quantitative estimations of vaginal fluid balance Clinical studies included basal temperature records, repeated vaginal smears and vaginal and cervical specimens for physical and chemical studies and for phase determinations

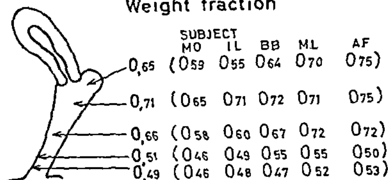


Fig 3 Average values for the water contents in different parts of the vagina Individual values are given in brackets

In addition, several observations were made on a number of other patients at the out patient clinic of the gynæcological department

Gravimetric measurements of secretion and reabsorption rates

The secretion rates into the different parts of the vagina were measured after temporary division of the vaginal cavity into segments with the aid of rubber membranes (commercial diaphragms fig 2) The segments were filled with absorbent material (cotton or commercial menstrual tampons) The out flow from the vagina was measured by means of absorbent material gauze layers covered by an outer layer of thin thight closing plastic All the absorbent materials were weighed before and after use The subdivision of the vaginal cavity into segments could not be performed in an exact reproduceable manner from time to time or from one patient to another, but the method used appeared to be the best of several methods tried Variations in the position of the membranes are due to the influence of different degrees of filling of the bladder and rectum changes in intrapelvic topography and changes between upright and lying

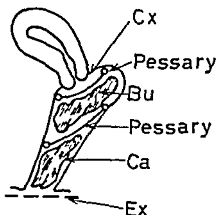


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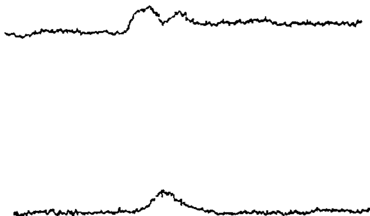


Fig 5 Proton magnetic resonance signals in one case (I.L.) obtained at the time of ovulation as determined by basal body temperature, cervical mucus arborization and vaginal cytology The upper record is from an 130 μg cell sediment obtained from bulbus vaginæ and shows the occurrence of two peaks indicating a barrier for water in cell membranes The lower record is from a 100 μg cell sediment from the recessus vaginæ and does not show any evidence of a barrier for water molecules Recordings performed at 47 Mc/sec

Sites of vaginal reabsorption

The next step in the investigation was to find indications of the sites of vaginal reabsorption of liquid material Some information on this subject was obtained by analyzing the water percentage of the intravaginal contents at different locations in the vagina The sampling was performed by suction of quantities amounting to about 10 mg into glass tubes which were introduced into the vagina in a direction and to a depth previously determined for each woman and adapted to her anatomy The average results from 5 normal cases are collected in Fig 3 The results strongly indicate that reabsorption of water may occur in the lower parts of the vagina and probably to a large extent in the vaginal recessi

In one normal case an experiment was sucessfully conducted in which a specially formed Pyrex glass tube was inserted in the vagina (Fig 4) to a depth of 4 cm and was carried by the patient

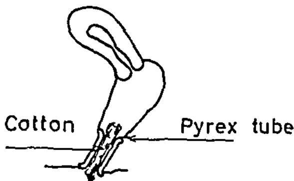


Fig 4 Position of Pyrex glass tube in the vaginal canal during experimental mechanical blocking of vaginal reabsorption

positions In addition, cyclic changes and individual anatomic differences may be sources of error The most commonly used arrangement is shown in Fig 2, allowing the measurement of (1) cervical secretion rate, Cx (with a small admixture of vaginal secretion), the secretion rates from (2) bulbus vaginæ, Bu, and (3) from canalis vaginæ, Ca Finally (4) the external discharge, Ex, was sampled as described above

The results of quantitative measurements are collected in Table I, in which the partial and total production rates in different sections of vagina are given The total rate of fluid production is the sum of the partial contributions The corresponding natural discharge rate, measured one day before and one day after the intravaginal measurements is also given The differences give the best available indication of the reabsorption rate and are also quoted In the group of normal women the natural external discharge rate is significantly smaller than the production or secretion rate The difference indicates the rate at which vaginal fluid disappears from the vaginal cavity before the fluid leaves the body It seems therefore certain that reabsorption really takes place in the vagina of normal women but in cases of chronic non-specific vaginitis this reabsorption appears to be reduced The increased external discharge encountered in these cases of vaginal inflammation appears, therefore, not to be due to increased secretion rate but to reduced reabsorption of liquid material from the vagina

dicated in Fig 5 and show a definite difference between the upper and lower epithelial cells

Discussion

The gravimetric determinations give conclusive evidence that in normal women there is a measurable reabsorption of material from the vaginal lumen As about 2/3 of the normal daily production at midcycle was reabsorbed it must be comprised mainly of water This conclusion is also supported by the fact that the water content is reduced as the material passes down the vagina This observation, together with the different net production rates in different sections of vagina strongly indicates that the lower part of the vagina the *canalis* and the *recessi vaginæ* play a dominant role in water reab orption Mechanical blocking of these parts also seem to inhibit reabsorption and proton magnetic resonance studies indicate a more rapid water exchange over epithelial cells from the lower vagina than from the upper vagina

In chronic vaginal inflammation of non specific type (i *e* no evidence of trichomoniasis gonorrhœa or fungi) the reabsorption appears to be reduced This reduced reabsorption seems to be responsible for the increased vaginal discharge noted by the patients and measured quantitatively Reabsorption of water is a process known to occur at many locations in the body in the spinal canal in the lower parts of the nephron and in the colon The results of this study seem to add a hitherto unknown location to this series of organs It is of some interest to compare quantitatively the reabsorption rate in the lower vagina with other known similar mechanisms The total mucosal area in the vaginal canal and recessi amounted as direct measurements indicate, to about 40 cm^2 in the normal cases The average migration therefore amounted to about 0 005 g/(hour × cm^2) a figure of a similar order of magnitude as for the colon (Starling 1941) In the cases of chronic inflammation part of the depressed reabsorption appears to be due to a smoothing out of the mucosal folds, thus causing a reduction of the available area of reabsorption to 1/2 or less as compared with the normals Functional changes of the vaginal epithelium may also occur but no evidence has yet been

Table I *Secretion and Absorption Rates of Liquid Material in g/hour*

	Normal Cases	Cases with Chronic Non-specific Colpocervicitis
Number of cases	12	7
Cx Secretion rate from cervix	0 11	0 10
Bu " " " bulbus vaginæ	0 10	0 05
Ca " " " canalis vaginæ	0 02	0 02
Ex External secretion rate during fractional sampling	0 01	0 03
Sum Total rate	0 24 ± 0 03	0 20 ± 0 03
Normal external discharge	0 06 ± 0 03	0 18 ± 0 03
Difference = reabsorption	0 18 ± 0 04	0 02 ± 0 02

for 24 hours This arrangement served to block the proposed reabsorption region by mechanical occlusion of vaginal recessi and canalis vaginæ In this case the outflow was of the same order as the total secretion rate, namely 0 22 g/hr, while, on the day before and after this experiment, the external secretions were only 0 06 and 0 07 g/hr This result suggests that in this case the vaginal fluid produced from cervix and bulbus vaginæ could not be reabsorbed due to the mechanical blocking

Nuclear magnetic resonance studies

In earlier investigations (Odeblad, 1959, 1960) strong evidence has been presented that the proton magnetic resonance signals from vaginal epithelial cell sediments are split into two components at maximum cornification due to the establishment of a barrier against water in the cells When material was examined from different parts of the vagina the vaginal epithelial cell suspensions from the lower part of the vagina appeared not to show such a splitting A more careful investigation was therefore undertaken By localized and gentle abrasion minute quantities of material of high degree of cytologic purity were obtained and were subjected to NMR spectrometry The results are in-

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THE EFFECT OF ŒSTROGEN ON THE ACID-SOLUBLE NUCLEOTIDE CONTENT OF THE RABBIT VAGINA

BY

LARS PHILIP BENGTSSON, ADAM DEUTSCH AND ROY NILSSON

Studies on the metabolism of phosphorus compounds in the rabbit uterus revealed an increase in the acid soluble compounds after several days of œstradiol treatment (Borell, 1951 a, b, Szego and Roberts 1953). Also an increase in acid labile phosphates in the rat uterus was observed during pregnancy as compared with the uteri of castrated animals (Walaas and Walaas, 1951 a, b). An increase in the acid soluble phosphorus content of the rabbit vagina has also been demonstrated, following a single injection of œstrogen (Bengtsson 1953). Furthermore, it has been shown that higher levels of ATP occur in the rabbit uterus after œstrogen treatment or during œstrus, as compared with the levels obtaining in immature animals (Menkes and Csapo 1952, Corner and Csapo 1953) and an early œstrogen induced increase is found in the acid soluble nucleotide pool of the rat uterus, especially in relation to uridine derivatives (Jervell *et al.* 1958, Mueller *et al.*, 1958, Gorski and Mueller 1963). In addition, a marked increase of ATP and of the sum of the guanosine and uridine phosphates has been found in the rat uterus after 20–160 hours of œstrogen treatment of immature animals or of ovariectomized adult animals (Volfin *et al.* 1961).

The following abbreviations are used: A = adenosine, G = guanosine, C = cytidine, U = uridine, MP = 5'-monophosphate, DP = 5'-diphosphate, TP = 5'-triphosphate, NAD = nicotinamide-adenine dinucleotide (diphosphopyridine nucleotide), TCA = trichloroacetic acid.

found for such a mechanism NMR, in one case, did not show increased blocking of water penetration rate over the cell membrane

This investigation has, as far as is known to the author, presented new aspects on the problems associated with vaginal inflammations and discharge Some evidence has also accumulated on the existence of cyclic variations in the intravaginal fluid balance and on developmental factors causing changes after puberty and menopause in the reabsorbing capacity of the vagina Data has also been collected in cases with trichomoniasis infections and other types of vaginal infections All these studies have currently been extended and will be reported later It is hoped that these new aspects may lead to better understanding of vaginal physiology and form a basis for improved diagnosis and treatment of vaginal affections

SUMMARY

The human vagina is composed of two anatomically different parts, an upper sac and a lower canal with pockets directed forwards on each side of the urethra The vaginal canal and the pockets have been shown to reabsorb a large part of the liquid contents secreted into the vaginal lumen from the cervical glands and the desquamation of the epithelium in the upper vaginal sac The externally observable discharge is the difference between the secreted and the reabsorbed amounts Investigations on 12 healthy volunteers indicated that the total secretion rate normally amounted to about 6 g/day and the normal reabsorption rate to about 4 5 g/day Investigations on 7 cases of longstanding non specific vaginal inflammation with increased external discharge indicated that the total secretion rate was not affected but the reabsorption was reduced to negligible values

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doses of œstrogen 50 μg of Dimenformon (Pharmacia) intramuscularly daily for 7 days This treatment produced a marked hypertrophy of the uterus and the vagina

The animal was decapitated and the vagina was removed within 30–50 seconds and frozen on a special freezing table (Bengtsson 1953) When frozen, thin chips were scraped off with a scalpel and without preliminary thawing they were subjected to triple extraction with 5 % (w/v) TCA at 0° C Finally, the acid filtrate was brought to pH 6 by repeated washings with ether, and freed from ether by passing nitrogen through the extract All these procedures, and also determination of the tissue dry weight and tissue nitrogen, were performed according to the methods of Bengtsson (1962)

Ion exchange chromatography

The protein free vaginal extracts of pH 6 were adsorbed either on Ecteola or on Dowex 1 columns

For chromatography on Ecteola, the instructions of Nilsson and Sjunnesson (1961) were followed Ecteola cellulose (Whatman) in powder form was suspended in water and freed from fines by decantation A dilute suspension of the powder was poured into a column and allowed to settle under gravity The column (1 cm×25 cm) was washed with 200 ml of M triethylammonium acetate (pH 6) and then with water to remove excess triethylammonium acetate The vaginal extract, containing 80–200 optical density units at 260 mμ was then run through the column After adsorption the column was washed with three bed volumes of water Elution was performed using a linear gradient (0–0 6 M) of triethylammoninum acetate (pH 6) The flow rate was 1–2 ml/min The optical density of the eluate was read continuously at 254 mμ in an LKB Uvicord Ultraviolet Absorptiometer The effluent was then collected in 15 ml aliquots in a fraction collector

To facilitate direct comparison with the results of Bengtsson (1962) in one group of experiments an aliquot of the extracts of 30–60 optical density units was subjected to chromatography on Dowex 1 in the formic acid system of Hurlbert et al (1954) as described in detail by Bengtsson (1962)

In a recent study of the time sequence in the effect of œstrogen on the rabbit vagina, Bengtsson (1962) demonstrated changes in the relative proportions of the major nucleotide fractions in the vaginal extracts following castration and subsequent œstrogen treatment The maximum effect was obtained after 7–11 days of œstrogen treatment The different fractions were separated by ion exchange chromatography as described by Hurlbert et al (1954) but were identified only by elution position in comparison with standard samples without further purification and analysis of the fractions

In the present work, the investigations of Bengtsson (1962) are carried further by a detailed spectrophotometric and chemical analysis of the major individual nucleotide components, obtained in this case by ion exchange chromatography on Ecteola columns and subsequent paper chromatography of complex fractions By these methods a comparative assay was made of the ultraviolet-absorbing material and particularly of the acid-soluble nucleotide content of the vagina from normal, castrated and œstrogen treated, and castrated untreated rabbits The results apply to the four major components which were fully identified as NAD, AMP, ADP and ATP In the case of œstrogen treatment of castrated rabbits the steroid was administered for 7 days which, according to Bengtsson (1962), results in a maximal effect.

Material and Methods

Fully mature rabbits of mixed breed, weighing 2 5–4 2 kg were used for the experiments The animals were kept and fed as described by Bengtsson (1962)

A non-treated, mature, normal, female rabbit is in a state of more or less continuous œstrus, it is not known if minor variations in the endocrine condition of the genital organs occur during this protracted œstrus or during the life of the mature female rabbit However, it may be assumed that all normal, non-treated rabbits were in the same endocrine condition

Castration was performed 2–3 weeks before the experiments For technical details see Bengtsson (1953)

To obtain pronounced œstrogen stimulation of the genital organs, the animals in the hormone treated group received large

doses of œstrogen 50 μg of Dimenformon (Pharmacia) intramuscularly daily for 7 days This treatment produced a marked hypertrophy of the uterus and the vagina

The animal was decapitated and the vagina was removed within 30–50 seconds and frozen on a special freezing table (Bengtsson 1953) When frozen thin chips were scraped off with a scalpel and without preliminary thawing they were subjected to triple extraction with 5 % (w/v) TCA at 0° C Finally, the acid filtrate was brought to pH 6 by repeated washings with ether, and freed from ether by passing nitrogen through the extract All these procedures, and also determination of the tissue dry weight and tissue nitrogen, were performed according to the methods of Bengtsson (1962)

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Identification of ion exchange fractions

Appropriate fractions of the effluent from the Ecteola columns were pooled and concentrated by lyophilisation, the residue was taken up in a small volume of water and fractionated by paper chromatography on Whatman No 1 filter paper The following solvent systems were used 1) isobutyric acid—ammonia (d 0 880)—water (66 1 33 parts), 2) ethanol—M ammonium acetate, pH 7 5 (70 30 parts), 3) n-propanol—ammonia (d 0 880) —water (60 30 10) and 4) isopropanol—saturated ammonium sulphate solution—water (2 79 19) The ultraviolet-absorbing spots were located by photography in ultraviolet light These spots were cut out and eluted with water for quantitative determination of the fractions Ion exchange fractions which gave more than one ultraviolet-absorbing spot on the paper chromatograms were resolved into the individual components by preparative paper chromatography in one of the above mentioned solvents

For the purpose of identification, the following analyses were performed with the individual components obtained either directly from the ion exchange fractions or after resolution by preparative paper chromatography 1) spectrophotometry at pH 1 and 14, 2) determination of total and labile phosphorus (after hydrolysis for 10 min, at 100°C in N hydrochloric acid (Allen, 1940)), 3) estimation of purine-bound pentose by the orcinol method of Albaum and Umbreit (1947), 4) determination of the position of phosphate groups in the nucleotides (2′, 3′ or 5′) by oxidation with periodate according to Dixon and Lipkin (1954) and 5) analysis of the purine bases and pyrimidine nucleotides obtained by hydrolysis in N hydrochloric acid at 100° C for one hour The products of hydrolysis were subjected to paper chromatography in solvent systems 1) and 4), as well as in 5) isopropanol-hydrochloric acid (d 1 18)—water (65 17 18) RF-values and spectrophotometry after elution of the spots from the paper with 0 1 M hydrochloric acid were used for identification and quantitative analysis The extinction coefficients of 14 500 and 10,000 were used at pH 1 and 260 mμ for adenosine and uridine derivatives respectively, and 17,000 for NAD at pH 7 and 259 mμ (Siegel *et al*, 1959) NAD was further identified

Table I. *Optical Density Units (O.D U) at 260 mu in TCA Extracts of the Rabbit's Vagina (Two Pooled Vaginæ in Each Group)*

Hormonal State of the Animal	(O D U) at 260 mμ	
	per g tissue dry weight	per g tissue N
normal	253	1770
castrated	171	1330
treated with œstrogen after castration	365	2190

by spectrophotometry after addition of potassium cyanide at pH 11 (Ciotti and Kaplan, 1957) and after reduction with sodium borohydride (Mathews 1948 Mathews and Conn, 1953) as well as with alcohol dehydrogenase in the presence of ethanol (Ciotti and Kaplan, 1957)

All analyses were performed in comparison with standard samples

Results

TCA extracts of the vagina of normal, castrated and œstrogen treated, and castrated untreated animals all gave ultraviolet absorption curves with a maximum between 257 and 260 mμ, and a minimum around 230 mμ typical of the absorption curves of adenine nucleotides Table I shows the amount of ultraviolet absorbing material in the extracts from a typical experiment Castration resultet in a decrease in the acid soluble ultraviolet absorbing material of more than 30 per cent per g dry weight as compared with the normal animal Œstrogen treatment, on the other hand resulted in an increase of more than 100 per cent as compared with the values after castration and without œstrogen Calculated in terms of tissue nitrogen the changes are less pronounced than expected because of the relatively high nitrogen content of the vaginal tissues of normal (14 4 per cent) and œstrogen treated (16 7 per cent) animals as compared with castrated ones (12 9 per cent of the dry weight) On this basis castration gives a decrease of 25 per cent and œstrogen treatment an increase of 65 per cent of the acid soluble ultraviolet absorbing material at 260 mμ

Table II *Analysis of the Major Acid soluble Nucleotides in the Rabbit Vagina (Two Pooled Vaginæ in Each Experiment)*

Hormonal State of the Animal	Number of Experiments	% of Total Optical Density at 260 mμ				Micromoles g Tissue Dry Weight			
		NAD	AMP	ADP	ATP	NAD	AMP	ADP	ATP
normal	2	6	8	16	24	1 0	1 4	2 8	4 2
castrated	4	7	18	15	13	1 0	2 9	2 4	2 1
treated with oestrogen after castration	6	6	10	17	19	1 7	2 5	4 7	5 8

Ion exchange chromatography of the TCA extracts on Ecteola cellulose columns showed that at least 97 per cent of the ultraviolet-absorbing material in all extracts is retained on the columns Gradient elution with triethylammonium acetate gave a quantitative recovery of the adsorbed ultraviolet-absorbing material in all cases As shown in Fig 1, five main fractions were obtained from all three types of extracts, four of which were identified as NAD, AMP, ADP and ATP respectively The fifth major fraction, eluted immediately after NAD, is not a nucleotide Investigation of this major component of vaginal extracts is reported in a separate communication (Bengtsson *et al*, 1964)

The four main nucleotide fractions account for 50–60 per cent of the absorption of the extracts at 260 mμ and Table II shows their relative proportions in the different extracts

In the TCA extracts the ultraviolet-absorbing material not accounted for by the five main fractions is distributed between several smaller peaks in the ion exchange eluate

The eluate preceding NAD contains only 1–2 per cent of the total optical density of the extracts at 260 mμ and has not been investigated

CMP, UMP, UDP-acetylglucosamine and UDP-glucose—if present—appear in the eluate between NAD and AMP (Nilsson and Sjunnesson, 1961), UDP-glucose sometimes partly contaminating the AMP fraction In the present experiments, only a small peak representing UMP and corresponding to 1–2 per cent of the total optical density of 260 mμ was detected in the area between AMP and the large, hitherto unidentified fraction follow-

Table III Analysis of the Major Acid soluble Nucleotides in the Rabbit Vagina by two Different Methods (Method 1 Gradient elution from Ecteola columns in the triethylammonium acetate system of Nilsson and Sjunnesson 1961 Method 2 Gradient elution from Dowex 1 columns in the formic acid system of Hurlbert et al 1954) (Two Pooled Vaginæ in Each Group)

Hormonal State of the Animal		Micromoles g Tissue Dry Weight				Micromoles g Tissue Dry Weight			
		NAD	AMP	ADP	ATP	NAD	AMP	ADP	ATP
normal	Method 1	1 0	1 4	2 8	5 2	6 8	9 5	19 3	36 5
	Method 2	1 4	1 7	2 3	5 3	9 8	11 8	16 0	36 9
castrated	Method 1	0 8	2 2	2 0	2 1	5 8	17 1	15 6	16 1
	Method 2	0 8	2 0	1 5	3 1	6 2	15 5	11 7	24 1
treated with œstrogen after castration	Method 1	1 6	2 6	4 7	5 7	9 8	15 5	27 9	34 1
	Method 2	2 2	3 2	5 0	8 6	13 2	19 2	29 9	51 5

ing NAD, from extracts of normal and œstrogen treated animals In the case of castrated animals 4–5 per cent of the total optical density at 260 mμ was eluted in this area and, furthermore, relatively large amounts of an UDP-derivative, accounting for up to 7 per cent of the optical density of the extract at 260 mu, were found in the elution position corresponding to that of UDP-glucose and contaminating the AMP fraction The extract from normal and œstrogen treated animals, on the other hand, gave a fairly homogenous AMP fraction, which contained only small amounts of the UDP-derivative

In model experiments with nucleotide mono-, di and triphosphates (Nilsson and Sjunnesson 1961) the ion exchange eluate appearing after AMP contains peaks in the order GMP, CDP UDP ADP GDP CTP, UTP, ATP and GTP In the present work the first peak closely following AMP was identified as GMP in the extract from normal animals (Fig 1 a) In the extracts from castrated and œstrogen treated animals (Figs 1 b and 1 c) no separate peak for GMP appeared the small amounts of GMP present in the eluates were detected as contaminants in the last tubes from the AMP fraction The area between AMP-GMP and ADP in the extracts from normal and œstrogen treated animals contained 11–12 per cent and from castrated animals

Table II *Analysis of the Major Acid soluble Nucleotides in the Rabbit Vagina (Two Pooled Vaginæ in Each Eperiment)*

Hormonal State of the Animal	Number of Experiments	% of Total Optical Density at 260 mμ				Micromoles/g Tissue Dry Weight			
		NAD	AMP	ADP	ATP	NAD	AMP	ADP	ATP
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Table III *Analysis of the Major Acid soluble Nucleotides in the Rabbit Vagina by two Different Methods (Method 1 Gradient elution from Ecteola columns in the triethylammonium acetate system of* Nilsson *and* Sjunnesson *1961 Method 2 Gradient elution from Dowex 1 columns in the formic acid system of* Hurlbert *et al 1954) (Two Pooled Vaginæ in Each Group)*

Hormonal State of the Animal		Micromoles g Tissue Dry Weight				Micromoles g Tissue Dry Weight			
		NAD	AMP	ADP	ATP	NAD	AMP	ADP	ATP
normal	Method 1	1 0	1 4	2 8	5 2	6 8	9 5	19 3	36 5
	Method 2	1 4	1 7	2 3	5 3	9 8	11 8	16 0	36 9
castrated	Method 1	0 8	2 2	2 0	2 1	5 8	17 1	15 6	16 1
	Method 2	0 8	2 0	1 5	3 1	6 2	15 5	11 7	24 1
treated with œstrogen after castration	Method 1	1 6	2 6	4 7	5 7	9 8	15 5	27 9	34 3
	Method 2	2 2	3 2	5 0	8 6	13 2	19 2	29 9	51 5

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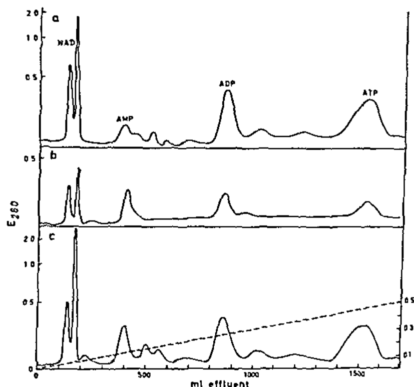


Fig 1 Chromatogram of the acid soluble material from the rabbit vagina on Ecteola columns (1×25 cm) (Two pooled vaginæ in each group) Left ordinate optical density units (O D U) at 260 mμ Right ordinate concentration of the eluant (triethylammonium acetate, pH 6)

a TCA extract (200 O D U) from untreated

b from castrated (80 O.D U) and

c from castrated rabbit vagina after œstrogen treatment (146 O D U)

8 per cent of the ultraviolet absorbing material In the case of normal and œstrogen treated rabbits the material in this area was divided between two peaks containing UDP-derivatives and a third peak containing UDP and derivatives of UDP, ADP and GDP The third peak was observed only in the extracts from castrated animals and then merely as an elevated baseline

The ultraviolet absorbing material in the area between ADP and ATP consisted of GDP, CTP, UTP and derivatives of UDP, ADP and GDP In the extracts from normal and from castrated œstrogen treated animals this area contained two peaks which accounted for 12–13 per cent of the optical density at 260 mμ

but in the extract from untreated castrated animals only one small peak containing 8 per cent of the ultraviolet absorbing material was found

In all extracts GTP was identified either as a minor contaminant in the ATP fraction or else as a small peak closely following ATP

Discussion

According to our analyses, NAD and the adenosine phosphates AMP ADP and ATP account for the major part of the acid-soluble nucleotide content of the rabbit vagina in all hormonal states Both NAD and the sum of the three adenosine phosphates decrease in amounts following castration and increase following œstrogen treatment, the changes corresponding in amount to those in the total ultraviolet absorbing material in the extract However there exist considerable variations within the group of the three adenosine nucleotides Castration results chiefly in the accumulation of AMP at the expense of ATP Subsequent œstrogen treatment induces a reversal of these changes

The results shown in Table II are in general agreement with those obtained by Bengtsson (1962) but whereas the figures in his paper represent crude fractions the figures in the present paper correspond to the amounts of the pure compounds free from other components

Table III gives a comparison of the values obtained for NAD, AMP ADP and ATP in one group of experiments for the same extracts from normal castrated and œstrogen treated rabbits by the method used in this paper (method 1) and by the method used by Bengtsson (1962) (method 2) The agreement between the two methods is reasonable but there exist certain divergences The NAD fraction obtained by method 2 includes the major non nucleotide fraction which is separated from NAD by method 1 Therefore method 2 gives figures for NAD which are too high especially in normal and œstrogen treated animals where the following major fraction occurs in significant amounts

Another point of divergence concerns the major adenine nucleotide fractions The figures given in Table III as obtained by method 1 represent the quantities of the pure components whereas

the amounts given by method 2 may include other components Expecially in the case of the ATP fraction large divergences may prevail between the two sets of results as the ATP fraction in method 2 also contains UTP, GTP and possibly also other substances

Next to adenosine derivatives, uridine nucleotides constitute the largest group of acid-soluble nucleotides in vaginal extracts Even if each of the individual uridine nucleotide fractions occurs in an amount insufficient for complete analysis, it can be stated that these fractions show the same shift toward less acidic compounds—being eluted at lower salt concentration— after castration as do the major adenosine phosphate fractions Of special interest is the disappearance following castration of the two largest individual uridine nucleotide fractions (which follow AMP in the extract from normal and hormone-treated animals) and the appearance of another uridine nucleotide, eluted at lower salt concentration and amounting to over 9 μmoles/g tissue nitrogen After œstrogen treatment this fraction practically disappears and the two uridine nucleotide peaks following AMP, appear in quantities totalling up to 18 μmoles/g nitrogen

Uridine derivatives account for 12 μmoles/g tissue nitrogen in the vagina of the castrated animals and the amount increases to 25 μmoles/g tissue nitrogen after œstrogen treatment This is a large increase, but less than that reported for the rat uterus by Mueller *et al* (1958) and by Gorski and Mueller (1963) for the early stages (0–4 hours) of œstrogen treatment It is also less than that obtained by Volfin *et al* (1961) for the sum of uridine and guanosine phosphates after 20–160 hours treatment with œstrogen

In different experiments, a total acid soluble nucleotide content of 90–130 μmoles/g tissue nitrogen was found in the vagina of rabbits in the normal state and in castrated, œstrogen-treated animals In castrated untreated animals this amount was reduced to 70–75 μmoles/g tissue nitrogen The ultimate changes following castration and œstrogen treatment in the small guanosine nucleotide fractions and in the even smaller cytidine derivatives could not be assessed

SUMMARY

The acid soluble nucleotides from the vagina of normal castrated and castrated œstrogen treated rabbits were separated by ion exchange chromatography on Ecteola columns followed by paper chromatography and spectrophotometric and chemical analysis of the individual components

Comparison of the nucleotide content of the vagina shows a substantial reduction after castration and a large increase following treatment with œstrogen

The changes in the content of NAD and the sums of AMP, ADP and ATP are approximately proportional to the changes in total nucleotide content The relative proportions of AMP, ADP and ATP, however, are markedly altered after castration, with accumulation of AMP at the expense of ATP Treatment with œstrogen results in a reversal of these changes

NAD AMP, ADP and ATP constitute four of the five major ultraviolet absorbing components in acid extracts of the vagina With regard to minor nucleotide fractions relatively large changes take place in three uridine nucleotide components Furthermore, a general shift toward less acidic components after castration and the reversal of these changes on subsequent œstrogen treatment is demonstrated

Acknowledgements

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ON A MAJOR ULTRAVIOLET ABSORBING COMPONENT IN ACID EXTRACTS OF THE RABBIT VAGINA

BY

LARS PHILIP BENGTSSON ADAM DEUTSCH AND ROY NILSSON

In the preceding communication (Bengtsson *et al* 1964) the presence of a major non nucleotide ultraviolet absorbing com ponent in acid extracts from the rabbit vagina was reported In the present work this component was further investigated with respect to its chemical nature and its occurrence in vaginal extracts from castrated and œstrogen treated rabbits

Material and Methods

Fully mature rabbits of mixed breed weighing 2 5 4 2 kg were used for the experiments Castration treatment with œstrogen removal of the vagina and its extraction with TCA were performed as described in the preceding communication (Bengtsson *et al* 1964) In several experiments also the uterus was removed within one minute of death and frozen either on the special freezing table used for the vagina or in liquid n trogen The frozen tissue was extracted with 5 % (w/v) TCA at 0° C as described for the vagina The ether used for the removal of TCA from vaginal and uterine extracts was freshly distilled after several hours shaking with FeSO, The extracts were freed from ether by bubbling nitrogen through the solution

Ion exchange chromatography was performed on Ecteola cel

The following abbreviations are used NAD = n cotinamide adenine d nucleotide (d phosphopyrid ne nucleotide) TCA = trichloroacetic acid

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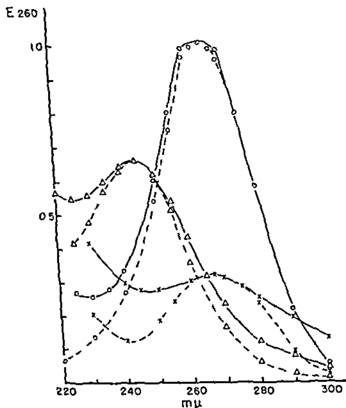


Fig 1 Ultraviolet absorption curve of the ion exchange fraction following NAD from TCA extracts of the rabbit vagina (——) in comparison with ascorbic acid ( ) o pH 6 △ pH 1 and + pH 10

tion Fig 1 gives a comparison of the absorption curves of ascorbic acid and of the corresponding fraction from vaginal extracts at different pH values Although the two curves are very similar at all the pH values investigated they are not completely identical This however is probably due to the presence of both the triethylammonium ion and impurities in the vaginal fraction Ion exchange chromatography of ascorbic acid under the same conditions as that of vaginal extracts gives the peak corresponding to ascorbic acid in an elution position identical to that of the

lulose columns according to Nilsson and Sjunnesson (1961). During exposure of the extract to the column and subsequent elution with triethylammonium acetate solution (pH 6) with a linear gradient (0–0.6 M) nitrogen was passed through both the liquid to be fractionated and the siphon used for the cutting of fractions. The optical density of the eluate was continuously recorded at 254 mμ in an LKB Uvicord Ultraviolet Absorptiometer coupled to a recording device.

Results

TCA extracts of the vagina of normal, castrated and œstrogen-treated rabbits gave ion exchange chromatograms corresponding to those given in Fig. 1 in the preceding communication (Bengtsson et al., 1964). Immediately following the NAD fraction a sharp peak was obtained in all experiments using extracts from normal and œstrogen-treated rabbits. In the case of castrated animals, however, NAD and the following fraction were not obtained regularly as clearly distinguishable separate peaks.

Although the shape of the ultraviolet absorption curve of the fraction following NAD is similar to that of a nucleotide, no purine or pyrimidine derivative could be detected before or after acid hydrolysis and subsequent paper chromatography. Phosphorus analyses were likewise negative. The most outstanding property of this fraction is the rapid disappearance of ultraviolet absorption on standing. The ultraviolet absorption of solutions containing this fraction can be prolonged by keeping the extracts and performing the chromatographic procedure under nitrogen. In the presence of 0.001 M cysteine at pH 6 the ultraviolet absorption is stable. On the other hand, the major fraction immediately following NAD is absent in ion exchange chromatograms of extracts from which TCA was removed with ether which was not completely free from peroxide. In the presence of 0.0002 M sodium periodate, the ultraviolet absorption disappears within 1–3 minutes.

The instability under oxidative conditions, together with the maxima of ultraviolet absorption at 265 mμ at pH 6 and at 245 mμ at pH 1, suggest the presence of ascorbic acid in this frac-

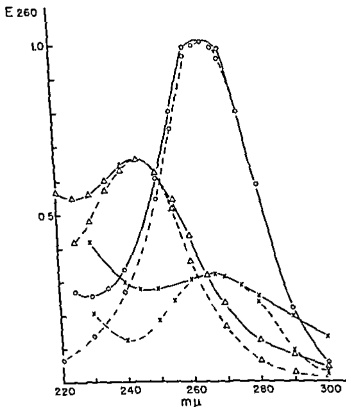


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Table I *Analysis of the Ascorbic Acid Content of the Rabbit Vagina and Uterus (Method 1 analysis of total TCA extract, Method 2 analysis of fraction obtained on ion exchange chromatography) (Two Pooled Organs in each Experiment)*

		Number of Experiments	% of Optical Density at 60 mμ	Micromoles/g Tissue Dry Weight
vagina from castrated rabbits	Method 1	4	13 8	2 9
	Method 2	4	6 4	1.4
vagina from rabbits treated with œstrogen after castration	Method 1	4	15 5	5 6
	Method 2	7	15 3	5 6
uterus from rabbits treated with œstrogen after castration	Method 1	3	16 8	7 3
	Method 2	5	12 9	5 6

fraction from vaginal extracts immediately following NAD Analysis of ascorbic acid in this fraction from several vaginal extracts by the dinitrophenylhydrazine method of Roe, Kuether, Desterling and Mills (Roe, 1954) gives the same values for the ascorbic acid content as those calculated from extinction at 260 mμ The extinction coefficient of ascorbic acid was determined immediately after dissolution in water saturated with nitrogen Under these conditions a value of 12,300 at 260 mμ was obtained

In several experiments, simultaneously with ion exchange analysis, an aliquot of the TCA extract was left exposed to air and the ascorbic acid content estimated from the decrease of the optical density at 260 mμ The value for ascorbic acid arrived at in this way was checked by analysis according to the method of Roe *et al*

TCA extracts from the rabbit uterus showed a decrease of optical density similar to that of vaginal extracts on exposure to air Ion exchange analysis revealed a fraction immediately following NAD and corresponding to ascorbic acid

Table I gives a comparison of the results obtained from the vagina and uterus of castrated rabbits following treatment with

œstrogen, with those obtained from the vagina after castration but without treatment with œstrogen

Discussion

The demonstration of a major non nucleotide ultraviolet absorbing component in acid extracts of the rabbit vagina and uterus is of importance for the analysis of the acid soluble nucleotide content of these tissues Its presence can falsify the values for total nucleotide content and especially for NAD, as shown by Bengtsson *et al*, 1964 (preceding communication)

Although not proven, this component of vaginal and uterine extracts has been tentatively identified as ascorbic acid The presence of ascorbic acid in the uterus is well known (Allen, 1939, Geroud, 1939) Increase of the ascorbic acid content of the uterus following œstrogen administration to castrated rats has been reported (Martini *et al*, 1950) On the other hand, in the intact mouse uterus, œstrogen decreases ascorbic acid concentration (Leathem 1959) In the present work, administration of œstrogen was found to increase the ascorbic acid content of the vagina of the castrated rabbit If measured in total acid extracts, this increase is only slightly larger than the corresponding increase in the total ultraviolet absorbing material of the extract However, the ascorbic acid fraction obtained after ion exchange chromatography of the acid extract is substantially larger after treatment with œstrogen than without this treatment The most likely explanation for these different results is a more rapid destruction of ascorbic acid in extracts from animals without œstrogen treatment This may indicate the presence of stabilizing factors in extracts from œstrogen treated animals

Comparison of the ascorbic acid contents of the vagina with the uterus of castrated rabbits after œstrogen treatment shows close resemblance between the two tissues

It is of interest from the point of view of a possible functional relationsh p of œstrogens to ascorbic acid that œstrogens seem to stimulate collagen synthesis This refers specifically to the hydroxylation of lysine and proline in the formation of collagen by the uterus of the ovariectomized rat according to a recent report

(Kao *et al*, 1964) On the other hand, Robertson and Hewitt (1961) have shown that *in vitro* addition of ascorbic acid to granuloma cells obtained from scorbutic guinea pigs stimulated collagen synthesis, as indicated by increased incorporation of radioactive proline into the protein Similar results were obtained by Stone and Meister (1962) using tritiated proline

SUMMARY

Acid extracts of the vagina of castrated rabbits contain a major ultraviolet-absorbing component which has been tentatively identified as ascorbic acid After œstrogen treatment the ascorbic acid content of the vagina increases This increase is approximately proportional to the increase in the total ultraviolet absorption and the total nucleotide content of the extracts The destruction of ascorbic acid is more rapid in extracts from castrated animals without treatment with œstrogen than following œstrogen treatment Acid extracts of both vagina and uterus from castrated rabbits show a similar ascorbic acid content after treatment with œstrogen

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THE COLPOSCOPICAL PICTURE OF TRICHOMONAS VAGINITIS

BY

PER KOLSTAD*

The clinical features of Trichomonas vaginitis are well known The patient usually complains of an offensive vaginal discharge which is often accompanied by intense itching and irritation of the external genitals On speculum examination the vaginal walls are more or less swollen and hyperæmic, and on the surface there may be enlarged papillæ which bleed readily—the straw berry vagina Strawberry like patches can, however, be found in vaginitis without trichomonal infection The ultimate diagnosis thus depends on the demonstration of the parasite under the microscope On the other hand the flagellate may be harboured in the vagina of women without typical clinical features A complementary method to help decide if active trichomonal infection is present may therefore be of value

There seems to be no general agreement upon the existence of a colposcopical picture characteristic of Trichomonas vaginitis Mestwerdt and Wespi (1961) claim that the appearance of the discharge as observed by colposcopy is nearly pathognomonic Cramer (1962) likewise in his textbook of colposcopy demonstrates a photograph of foamy secretions containing small air-bubbles as typical of trichomonal infestation The occurrence of red and white dots (rote und weisse Stippchen) has also been considered characteristic of trichomonal vaginitis (Michalzik, 1959) Holtorff (1961) interpreted these red and white dots as capillary ectasis and papillary hypertrophy, respectively

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In an extensive study of the colposcopical and histological patterns of Trichomonas vaginitis, Holtorff and Krimmenau (1960) described three different degrees of vaginitis which were relatively easy to recognize by colposcopy 1) a diffuse hyperæmia, 2) a diffuse and patchy hyperæmia and 3) a prominent patchy hyperæmia with formation of small lymph follicles However, similar pictures could be observed in cases of non specific vaginitis, although trichomonal infection accounted for between 90 and 95 per cent of the cases The authors concluded that the parasite did not induce a specific inflammatory reaction in the vaginal epithelium, but a non specific reaction of the vascular stroma with a secondary effect upon the epithelium

Koller (1963) reported an association between Trichomonas vaginalis cervicitis and the colposcopical finding of fork- or antler like capillaries termed double crested capillaries In a retrospective study Bergsjo, Koller and Kolstad (1963) demonstrated a positive correlation between the presence of the parasite in cytological smears and double crested capillaries in colpophotographs of the vaginal portio It was concluded that double-crested capillaries may be present in small numbers on the otherwise normal portio or may be caused by other agents than the flagellate However, the presence of large areas of double crested capillaries is a very strong indication of active trichomonal infection

The present study is a prospective investigation of the vascular pattern of Trichomonas vaginitis It is aimed at testing the pos sibility of a specific inflammatory reaction to the parasite mor phologically reflected in the appearance and arrangement of the capillaries on the vaginal portion

Terminology

On the normal portio vaginalis uteri two types of terminal vessels can be observed by colposcopy (Koller 1963) 1) *hair pin capillaries* and 2) *network capillaries* (Fig 1) The presence of hairpin capillaries depends upon the development of the connective tissue papillæ in the surface epithelium (Zinser and Rosenbauer 1960 Kos 1960, Mikolas *et al* 1962) Their

a)

b)

Fig 1 The terminal capillaries of the normal squamous epithelium of the cervix a) hairpin type, b) network type

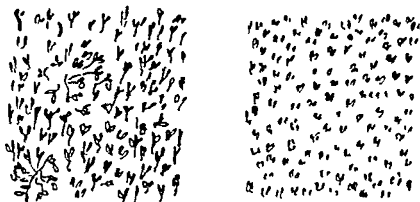


Fig 2 Schematic drawing of double-crested capillaries



Fig 3 Double-crested cap llaries in a case of Trichomonas vaginitis (colpophotograph)

shape is characterized by a fine ascending and descending branch lying close together and forming a smooth loop If the surface epithelium is not too thick and has a normal translucency and the angle of observation as related to the course of vessels is suitable the whole loop can be observed by colposcopy Often however the crest of the loop only is visible and the hairpin capillaries appear as small densely and regularly arranged dots

The term *double crested capillaries* will in the following as suggested by Koller (1963) be applied to terminal vessels of the hairpin type which show two or more crests at the top of the loop Their shape may be described as fork antler or cloverleaf like When the crests of the loops only are visible, the colposcopical picture sometimes may resemble the microscopical appearance of diplococci (Figs 2 *and* 3)

Material and methods

The *series investigated comprised* 391 patients examined in the Out patient Department of the Women s Clinic Karolinska Sjukhuset The diagnoses were as shown in Table I

Table I *Total Material Investigated 391 Cases*

Main Diagnosis	Number of Cases
Normal state	8
Vaginitis	32
Cervical polyp	13
Ectopy or ectropion	75
Ectopy and transformation zone	58
Transformation zone	87
True erosion	3
Condyloma acuminata	2
Leukoplakia	12
Metaplasia	15
Leucæmic infiltrate	1
Ovarian carcinoma	2
Dysplasia	24
Carcinoma in situ	34
Early invasive carcinoma	13
Invasive carcinoma	12
Total	391

Trichomonas vaginalis was found in 79 cases,
non specific vaginitis in 59 cases

In all the cases a clinical gynæcological examination was first performed A wet smear was diluted with physiological saline at body temperature and immediately examined under a low power *microscope for the presence of Trichomonas vaginalis* Thereafter two smears were taken with a wooden Ayre's spatula from the posterior fornix and the external os, respectively The slides were immersed in ether-alcohol fixation solution for 30 minutes and stained according to the method of Papanicolaou

Colposcopy was performed with a Zeiss colposcope at a *magnification* of $\times 16$, always employing a green filter The vaginal portion was rinsed with physiological saline before colposcopy Acetic acid, Schillers fluid or other irritating solutions were never used, because they disturb the translucency of the surface epithelium and thereby the picture of the *underlying terminal* capillaries In selected cases colpophotographs were taken according to the method of Koller (1963) In all 391 cases a sketch

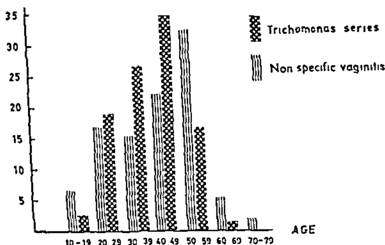


Fig 4 Age distribution of the Trichomonas series (79 cases) compared with the age distribution of patients with non specific vaginitis (59 cases)

of the vaginal portion was made on special sheets, and the presence of double-crested capillaries and their arrangement (scanty, diffuse patchy) noted

In 79 of the patients Trichomonas vaginalis was demonstrated either in the wet smear, in the Papanicolaou smear, or in both The rest of the series (312 cases) served as controls A group of 59 patients with non specific vaginitis served as a special control series

Results

As mentioned above 79 (21 0 per cent) of the patients had trichomonal infection The age distribution of these cases is compared in Fig 4 with that of the non specific vaginitis group (59 cases) Two patients (2 5 per cent) with trichomonal infection and four (6 8 per cent) with non specific vaginitis were below 20 years of age The majority of the Trichomonas cases occurred in the childbearing ages, while only 17 7 per cent were

Table II *The Correlation Between the Presence of Trichomonas Vaginalis in Smears and the Occurrence of Double Crested Capillaries*

Trichomonas Vaginalis *Present in*	Total Number	Colposcopy + No	*Per Cent*
Wet smear + Papanicolaou smear +	55	53	96 5
Wet smear + *Papanicolaou smear* —	7	6	85 6
Wet smear — Papanicolaou smear +	17	9	53 0
Wet smear — Papanicolaou smear —	312	5	1 6
Total	391	73	18 7

Colposcopical false negatives" 11 (13 9 %)
„ "false positives" 5 (1 6 %)

post-menopausal, as compared with 39 0 per cent post menopausal women in the non-specific vaginitis series

Of the Trichomonas patients 15 2 per cent were unmarried and exactly the same percentage had never been pregnant The corresponding figures in the special control series were 27 1 and 22 0 per cent respectively

The evaluation of the possible relationship between the colposcopical finding of double-crested capillaries and the presence of trichomonal parasites in wet smear, in the Papanicolaou smear, or in both is presented in Table II It must be emphasized that a positive colposcopy indicates that terminal capillaries of the double-crested type were observed either diffusely all over the portio and the vagina, or that characteristic patches of such capillaries were spread out over a large area The finding of a few scattered double-crested capillaries or a few small patches with terminal vessels of this specific type was not classified as positive colposcopy

It can be seen from Table II that 11 cases of Trichomonas infestation were missed by colposcopy, and in 5 cases a false positive diagnosis was made This gives a false negative number of 13 9 per cent and a false positive of 1 6 per cent The largest



Fig 5 Intra-epithelial double-crested capillaries in a case of Trichomonas vaginitis before treatment

number of the false negatives (8 cases) belonged to the group where the parasite could not be demonstrated by direct microscopy but was found in the Papanicolaou smears only Further more four of the patients which harboured the flagellate in the vagina were symptomfree and three sought gynæcological advice not because of discharge but because of irregular periods In none of these seven cases were typical double crested capillaries observed by colposcopy If we assume that these women did not have an *active* trichomonal infection the false negative number was only 4 cases or 5 6 per cent Also of some significance may be the observation that four of the patients in the false negative group two with and two without symptoms were postmenopausal It is possible that the Trichomonas flagellate cannot induce a specific vascular reaction without the epithelium being prepared by œstrogens

By close scrutinizing of the records of the false positive cases was found that in none of them was the vascular pattern described as quite typical of trichomonal vaginitis By colposcopy

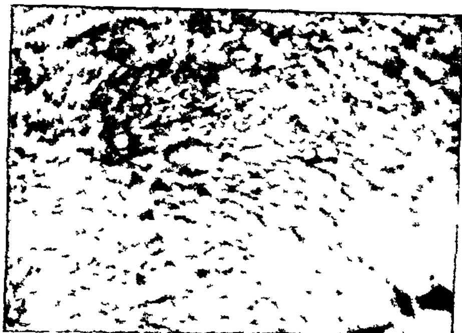


Fig 6 Colpophotograph of the same area of the vaginal portion as shown in Fig 5 three weeks after treatment with metronidazole

was either observed few and scattered double-crested capillaries, or the shape of the vessels was not definitely fork or antler like All five cases apparently had been classified as doubtfully positive at the initial colposcopical examination

The patients and their partners were treated with metronidazole for one week, and the effect of the treatment upon the terminal capillaries of the surface epithelium studied Within one week the dilatation of the vessels disappeared more or less within two weeks the double-crested capillaries were no longer easily observable, but up to five weeks after treatment some capillaries of this specific type could still be seen (Figs 5 and 6) In one case the vascular pattern did not change in spite of two courses of metronidazole medication to the patient and her husband In this special case however numerous *flagellates* were found both in wet smear and in Papanicolaou smears two weeks after completion of the second course of treatment This case thus represented a metronidazole-resistant Trichomonas infection

Discussion

The present study strongly supports the earlier works by Koller (1963) and by Bergsjo, Koller and Kolstad (1963) on the relationship between Trichomonas vaginalis infestation and the occurrence of double crested capillaries on the portio In the paper by Holtorff and Krimmenau (1960) three different degrees of inflammatory reactions were described in trichomonal vaginitis The colpophotographs reproduced in their paper seem to show that in all three types numerous double-crested capillaries were present, although the pictures do not clearly reveal the single terminal vessels However, the histological part of their study demonstrated that trichomonal inflammation was characterized by an increased vascularity of the squamous epithelium with elongation of the connective tissue papillæ and the occurrence of intra epithelial dilated capillaries The same observation was made by Koss and Wolinska (1959), and these authors stated that the epithelial vascularity was completely out of proportion to the inflammatory processes in the underlying stroma thus suggesting an extrinsic irritation by the parasite A comparison with a cervicitis control group revealed significantly less epithelial vascularity in the absence of Trichomonas vaginalis

On the basis of the above mentioned earlier studies and the results of the present investigation it seems justified to conclude that Trichomonas vaginalis in the œstrogen prepared vaginal epithelium induces a specific vascular reaction, morphologically reflected in the massive occurrence of intraepithelial capillaries of the double-crested type In post menopausal women this reaction is not always seen neither is it found in asymptomatic Trichomonas infestation

SUMMARY

In a series comprising 391 patients with different gynæcological disorders the possible correlation between Trichomonas infection and the occurrence of intra epithelial fork , antler- or clover leaf like terminal vessels termed "double crested capillaries was studied In 68 out of 72 cases with *active* tricho-

monal infection this specific vascular pattern was observed by colposcopy, while only 5 out of 312 control cases showed a vascular picture of similar type It is concluded that Trichomonas vaginalis induces a specific vascular reaction in the œstrogen-prepared vaginal epithelium of pre-menopausal women The findings may be of significance in the clinical (colposcopical) diagnosis of active Trichomonas vaginitis

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PELVIC VARICOSITIES IN WOMEN

A preliminary report

BY

KARL-OLOF EDLUNDH

This paper is a preliminary report on some observations bearing on a possible connection between chronic pelvic pain and venous stasis in the pelvis, or, as it is also called, pelvic varicocœle Chronic pelvic pain has for a long time been associated with venous stasis (Faure and Siredey 1928, Castano 1931 Stajano 1934, Taylor 1949 Crottogini 1953, Fegerl and Narik 1954 Taylor 1957), and the pelvic congestion syndrome now seems to be a well established entity

It is common to differentiate between primary and secondary venous stasis The stasis usually is localized to one or both ovarian pedicles and the uterus Secondary venous stasis often accompanies various pathological processes in the pelvis, *e g*, tumours and chronic inflammatory conditions The varicosities are supposed to appear early in the disease process Primary venous stasis on the other hand, is assumed to appear at a rather late stage This view however is not confirmed experimentally and on the whole it may be said that the ætiology and pathogenesis of primary venous stasis are obscure

It has also been known for several years that pelvic varicosities can be visualized by the injection of radiopaque medium into the pelvic vessels (Topolanski-Sierra 1958 Helander and Lindbom 1960 Hughes and Curtis 1962) A considerable improvement in the study of this vascular region was achieved by the introduction of a special rœntgenological technique *viz* selective angiography of the left renal vein This

method for investigation of pelvic varicosities has been developed by Ahlberg, Bartley and Chidekel With this technique it is possible to show that in some women there occurs a retrograde passage of the radiopaque dye through the left ovarian vein and that this is often combined with the filling of huge varicosities in the ovarian and uterine pedicles Furthermore, it can be seen that in these patients the ovarian vein is often greatly dilated, and that in those cases where the vein has valves when entering the renal vein, such valves are incompetent (Ahlberg, Bartley, Chidekel and Edlundh 1964)

On the basis of these investigations pelvic varicosities may be identified as a retrograde passage of the radiopaque medium and by the filling of varicosities in the left or both ovarian pedicles and in the broad ligament According to anatomical text-books the right ovarian vein enters the right renal vein in about 5–10 per cent In these cases it should be possible to obtain a similar rœntgenological picture on the right side However, incompetence of the right ovarian vein has not yet been demonstrated with this technique

The problem that will be discusssed is the possible relation between rœntgenologically diagnosed varicosities and certain gynæcological complaints

Material

Thirty-four women, para I–V, admitted for investigation of chronic pelvic pain, were examined using selective angiography of the left renal vein The rœntgenological examination revealed that 21 patients had pelvic varicosities according to the definition above The X-ray findings in one of these patients are seen in Fig 1 Ten women, para O–V, admitted to the department because of meno-metrorrhagia but without any complaints of pelvic pain were also examined by the same technique In this group no pelvic varicosities were found

Age incidence

The age varied from 28–55 years One of the patients 55 years old had her last period 12 years previously All the other women



F g 1 Selective ang ography of the left renal vein (para IV) The p cture is taken 10 sec after the injection of the radiopaque dye Retrograde f'l ing of the left ovarian ve n and b lateral varicos ties in the parametrium.

were menstruating The great majority were in their thirties and forties This is in accordance w th other authors findings of the age incidence for the pelv c pain syndrome (Benson Hanson and Matarazzo 1959) Further information is given in Fig 2

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Table 1 *The Most Common Symptoms in Order of Frequency in 21 Women with Pelvic Varicisities*

Symptoms	Number of patients
Lower abdominal pain	19
Deep dyspareunia	15
Secondary dysmenorrhea	13
Urgency	13
Meno-metrorrhagia	12
Feeling of heaviness in the lower abdomen	11
Nervous complaint	8

Symptoms and signs

The most common symptoms occurring in patients having rœntgenologically confirmed varicosities were abdominal pain, secondary dysmenorrhœa, deep dyspareunia, and a feeling of heaviness in the lower abdomen The abdominal pain was localized either suprapubically or in one or both iliac regions with some preference for the left side The secondary dysmenorrhœa as a rule started 7 to 10 days before an expected period The deep dyspareunia in some cases was so pronounced that it caused total frigidity A striking finding among a majority of the patients was the great number of nervous complaints such as depression headache and insomnia This observation has also been made by others (Duncan and Taylor 1952, Taylor 1954 Benson Hanson and Matarazzo 1959) and is probably the explanation for the view of quite a few gynæcologists to regard this pain syndrome as a psychosomatic disease Bladder symptoms of so called urgency type were another common complaint Cystoscopy sometimes showed a trigonic cystitis No bacteriuria was found The duration of symptoms varied widely between different patients but typically they started after the last delivery Some of the patients first noticed a period of indistinct pain but later the typical picture with dysmenorrhœa dyspareunia and heaviness in the lower abdomen appeared Table 1 shows the symptoms in order of frequency of the 21 patients As can be seen there is a variety of symptoms in most of the patients It is easy to miss the diagnosis if the cardinal symptoms just mentioned are not kept in mind

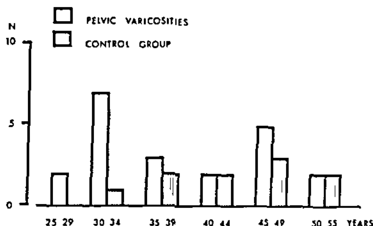


Fig 2 Age distribution of the patients with pelvic varicosities and of the control group

Marital status and parity

Of the 21 patients in the varicosity group all were married except one who was divorced Obstetrically they had a total of 55 children, 7 spontaneous abortions and 2 legal abortions Fig 3 shows the parity of these 21 patients and the 10 patients in the control series As can be seen from Fig 3 there are no nulliparæ among the patients with positive X-ray findings

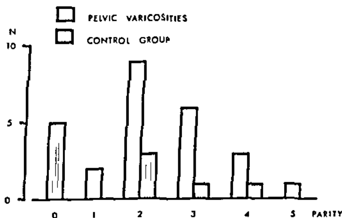


Fig 3 Parity of the patients with pelvic varicosities and of the control group

and then stripped down to the ovarian pedicle, the smaller vessels entering the ovarian vein being ligated

Results

The time of observation is still too short and the series too small to permit any definite conclusions One symptom that seems to disappear at an early stage is the deep dyspareunia Furthermore, there are two patients with menorrhagia who stated that their periods became shorter and scantier after the operation All patients stated that they had experienced some degree of pain relief

It may be argued that the results of such an operation may be jeopardized by long standing venous stasis with irreversible damage in the tissues concerned It is too early to express an opinion In one case scarring and fibrosis of the uterosacral ligaments were observed It is possible that the operation mentioned above must be extended to include section of the uterosacral ligaments Only further clinical trial can give the answer to these problems

Discussion

There are several theories about the mechanism underlying pelvic varicosities Insufficiency of the valves of the left ovarian vein with retrograde passage of the blood, especially in the standing position appears to be one important cause The results of the rœntgenological technique employed in this study strongly indicate such a pathogenesis As to ætiological factors the observation that no pelvic varicosities were found in the non *parous* women suggests that pregnancy is a relevant factor

A relationship between pelvic varicosities and the pelvic pain syndrome appears to exist in some patients A pathogenetic con nection seems to exist in those patients where symptoms such as secondary dysmenorrhœa deep dyspareunia, pelvic abdominal pain and heaviness are found together with rœntgenologically verified varicosities and where other possible causes have been eliminated after careful examination of the patient

At the gynæcological examination notable findings are tender and sometimes enlarged ovaries, tenderness of the parametria, especially when the uterus is elevated, and tenderness of the uterosacral ligaments when these are stretched The cervix often is hypertrophied, cyanotic, and slightly eroded Often there is *hypersecretion from the cervix* The uterus sometimes is enlarged and soft In a few patients, however, the findings were completely normal

Differential Diagnosis

Beause of the great number of unsuccessful surgical procedures developed for the treatment of chronic pelvic pain there is a great need for exact diagnosis The most common differential diagnoses are endometriosis and chronic salpingitis However, *diseases of the spine, particularly of the intervertebral discs,* and of the sacroiliac joints must be considered Affections of the colon and diseases of the urinary tract must also be excluded Of the 21 patients only 10 had pelvic varicosities as the sole finding In the other cases the varicosities appeared together with other diseases such as chronic salpingitis, degeneration of the intervertebral discs, Bechterew s disease, relaxation of the pelvic floor, endometriosis and myoma of the uterus It is conceivable that *in such cases it is difficult or even impossible* to elicit the real cause of the symptoms

In order to establish a diagnosis the routine examination of these patients must include urine analysis, intravenous urography, X-ray examination of the colon, cystoscopy, and laparoscopy Orthopædic, neurologic and psychiatric consultations are also important steps in the evaluation of the patients

Therapy

Six patients in whom the only pathological finding was rœntgenologically verified pelvic varicosities underwent conservative operation with a special technique The left ovarian vein was ligated about 10–15 cm below its entrance into the renal vein

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A surgical procedure for the possible therapy of such patients is described As pelvic varicosities and possible sequelæ of this condition often occur in patients between 30 and 35 years old a conservative surgical approach has been attempted With more experience it may be found valuable to individualize the surgical treatment, *including more radical procedures* The importance of early diagnosis is discussed Further studies are in progress

SUMMARY

Thirty-four women, para I–V, admitted for investigation of chronic pelvic pain and having symptoms and signs of pelvic congestion syndrome were investigated using a special rœntgenological technique, *viz*, selective angiography of the left renal vein Twenty-one patients were found to have pelvic varicosities The rœntgenological examination revealed the varicosities to be caused by an insufficiency of the left ovarian vein with retrograde passage of the blood This insufficiency was often due to incompetent valves in the left ovarian vein at the entrance into the left renal vein

The results indicate that a relationship exists between pelvic varicosities and chronic pelvic pain in some patients An operative procedure is described for the possible cure of these patients Further studies are in progress

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THE INTERPOSITION OPERATION OF SCHAUTA-WERTHEIM-WATKINS FOR UTERINE PROLAPSE

A Follow up Study

BY

PER HENNINGSEN AND HARRY BROCKS

A number of studies in recent years have commended the interposition operation of Schauta-Wertheim-Watkins for the repair of uterine prolapse (Berger, 1961, Nabriski and Zeeloof, 1962, Granjon and Chevalier, 1961) This led us to review a series of 251 patients from surgical department B of the Diakonissestiftelsen Hospital, where this operation was the procedure of choice from 1939–1956

Indications and technique

The indications were uterine prolapse of varying degree, 62 cases of 1st degree cervix above the vulva, 128 cases of 2nd degree cervix reaching or just outside the vulva, and 125 cases of 3rd degree total prolapse 29 patients had cystocele only, 7 patients could not be classified (Table I)

The technique was that originally described by Wertheim (Wertheim, 1899), as later modified by Schauta (1903) Watkins published his method simultaneously with Wertheim in 1899

All patients who were still menstruating and a few with a recent menopause were sterilized by ligation of the tubes after obtaining the patient s consent (59 patients) Amputation of the

Table I *Indications*

Degree of Prolapse	No of Patients	
1st	62	25
2nd	128	51
3rd	25	10
Only cystocele	29	11
Unclassified	7	3
	251	100

cervix was performed where indicated, namely, when cervical hypertrophy was found (22 patients) Partial resection of the uterus was carried out if the latter was asymmetrical or was estimated as being too big (together with myomectomy a total of 37 patients) Colpoperineorrhaphy was performed when even a slight degree of rectocele was present, which amounted to almost every case (239 patients)

Anæsthesia was in all cases spinal anæsthesia sometimes supplemented by nitrous oxide or ether

Material

The series originally comprised 297 patients whose age distribution corresponds to that found in similar series from other departments (Jakobsen *et al*, 1961, Tophøj and Riber Christensen 1959) Approximately 60 per cent were in the age group 40-60 years The average age was 52 years ranging from 26 to 75 years

The immediate postoperative complications were as follows one patient died in the postoperative period (from coronary occlusion) Sixteen patients had pyrexia—temperature above 38° C for more than 48 hours—without obvious cause Twelve patients developed phlebitis of the lower extremities and pulmonary infarction occurred in three of these Thirty one patients had local complications in eleven cases infection in two wound rupture in two hæmatoma and in 16 cystitis this latter figure including only cases of cystitis requiring treatment (the patients were catheterized several times daily during the postoperative period until spontaneous micturition occurred (Table II))

Table II *Complications (251 Patients)*

	No of Patients	%	Recurrences
Death (coronary occlusion)	1	0 4	
Pyrexia (> 38° C for > 48 hrs)	16	6 4	
Phlebitis	12	4.8	
Pulmonary embolism	3	1 3	
Locally			
Wound infection	11	4.4	7
Wound rupture	2	0 8	0
Hæmatoma	2	0 8	0
Urinary infection	16	6 4	7
	31	12 7	14 (45 %)

The material available for follow-up comprises 264 patients, as there had been 27 deaths from causes unknown to us, and a further five patients could not be traced through the municipal registers Based on the answers to a questionnaire, the patients were classified into three groups 1) symptom-free, 2) those in whom it was possible to discover with certainty from hospital case records whether recurrence of the uterine prolapse had occurred, and 3) the remainder, who were asked to attend for gynæcological examination if there was any uncertainty in the replies to the questionnaire A further 13 patients had to be omitted following this analysis four patients who had undergone hysterectomy on account of other gynæcological diseases, five patients who had cancer of the cervix or corpus uteri, and four who gave uncertain answers to the questionnaire and refused to attend for gynæcological examination (Table III)

The material available for analysis thus comprised 251 patients One hundred (approximately 40 per cent) of these had prior to the operation had symptoms for more than three years Frequency of micturition was found in 116, and 54 had other urinary disturbances, such as urgency of micturition straining at micturition, abnormal micturition positions, etc (Table IV)

The average parity per patient was 2 7, which corresponds to the findings in the general population for the period in question Twelve patients were nulliparous, 32 had had more than four

Table III Material

Total number of patients		297
Death postoperatively		1
Deaths later		27
Untraceable		5
Omitted		
Hysterectomy due to other gynæcological diseases	4	
Cancer of the uterus	5	
Lacking cooperation	4	13
Total at follow up		251

Table IV Symptoms (251 patients)

	No of patients	
Pelvic pressure ≤ 3 years	93	
Pelvic pressure > 3 years	100	193
Back pain		54
Frequency of micturition		118
Cystitis		32
Other disturbances of micturition		54

Table V Deliveries (251 patients)

No of deliveries	0	1	2	3	4	5	6	> 6	Unknown
No of patients	12	46	67	54	32	12	5	15	8
Recurrences	4	10	19	14	13	4	2	2	5
%	33	22	28	26	40	33	40	13	63

deliveries, the largest number of deliveries being 12 (Table V) Complications of delivery and the birthweight of the infants could not be ascertained with certainty

Follow up

The criteria for recurrence were 1) patients who required a further operation 2) patients who had been treated with a pessary with relief of symptoms and 3) manifest—usually second degree—prolapse of the uterus or manifest cystocele at gynæcological examination When there was recurrence of both pro-

Table VI *Follow up*

	No of Patients	Recurrences
Questionnaire only	141	0
Examination by present authors	55	35
Examination by other hospitals	55	38
	251	73

Table VII *Treatment Prior to Operation*

	No of Patients	Recurrences	%
Pessary	59	20	34
Operation	11	2	24
Pessary + operation	6	2	
Total	76	24	31

lapse and cystocele, the patient was classified in the prolapse-group only

A gynæcological examination was performed by us in 55 cases (22 per cent) Fifty-five patients were examined in other hospitals, and in 141 patients the information obtained from the questionnaire was adequate, in a few cases supplemented by brief conversations (Table VI)

Seventy-six patients had previously been treated for uterine prolapse, eleven had been operated upon, 59 treated with pessary, and six with both modalities None had previously undergone an interposition operation (Table VII)

The average period of observation in patients without recurrence was 12 3 years, the longest 22 years, none were followed-up for less than five years The period of observation in patients with recurrence was calculated to the time of the recurrence (Table VIII)

Follow-up *examination revealed recurrences in* 73 *of the* 251 patients (one patient with two recurrences after two interposition operations *is included once in the analysis*) This gives a recurrence rate of 29 per cent Forty one per cent of the recurrences occurred within one year after operation, 75 per cent within seven years The remainder appeared with one to three

Table VIII *Period of Observation*

	No of Patients
0–10 years	115
10–20 years	127
> 20 years	10
	251

Average for patients without recurrences 12 3 years

Table IX *Time from Operation to Recurrence*

Years from operation to recurrence	2/12	12/12	2	3	4	5	6	7	8–13	> 13	unknown
No of recurrences in that year	12	18	4	9	1	5	2	4	per yr 1–3	3	3
Cumulative recur rences as % of total	16	41	47	59	60	67	70	75			

recurrences per year until twelve years after, and then one recurrence each in the 15th, 17th and 21st year, the latter being the longest interval between operation and recurrence In three patients the time of recurrence was uncertain (Table IX)

In patients with preoperative prolapse of first degree, there was recurrence in 19 per cent in prolapse of second degree 34 per cent and in prolapse of third degree 60 per cent Cases with cystocele as the sole indication for operation had 24 per cent recurrences (Table X) There was total prolapse in 10 per cent of the patients before operation (Table I) and in 33 per cent of the patients among the recurrences (Table X) This increased incidence is statistically significant ($P < 0.001$) There was a general tendency for the degree of prolapse at recurrence to be greater than prior to operation (Tables I and X), although ten patients with manifest prolapse of the uterus preoperatively recurred with cystocele only

Of 22 patients who underwent amputation of the cervix in the same session as the interposition operation, five (23 per cent) had recurrence of the prolapse A further two underwent re-amputation of the cervix without having recurrence of the pro-

Table X. *Degree of Recurrence*

Degree of Prolapse Prior to Operation	1st Degree	2nd Degree	3rd Degree	Cystocele	Unknown	Total	%
Total no of patients	62	128	25	29	7	251	
No of recurrences	12	38	15	7	1	73	
%	19	34	60	24	14		
Degree of prolapse at recurrence							
2nd degree	7	19	4	4	0	34	47
3rd degree	2	12	9	0	1	24	33
Cystecole	3	5	2	3	0	13	18
Unknown	0	2	0	0	0	2	2
						73	100

lapse Eleven patients underwent amputation of the cervix subsequent to the interposition operation, three of them experienced no recurrence of the prolapse Thus, five patients (3 + 2) who underwent subsequent amputation of the cervix had no recurrence of the prolapse, and eight patients (11 − 3) (11 per cent of the 73 cases of relapse) had cervical hypertrophy together with recurrence of their prolapse

Urinary incontinence (true as well as stress incontinence) was present in 44 patients before operation At the time of follow-up, incontinence was still present in ten patients, and recurrence of the prolapse in twelve This is a cure rate of 50 per cent Nine patients developed incontinence as a sequel to the operation (3 6 per cent of 251)

Other disturbances of micturition (as formerly defined) were found in 29 patients In twelve of them, physical examination provided no explanation for this (Table XI)

These twelve cases, together with the 19 with incontinence and the five with hypertrophy of the cervix, may be classified as relative recurrences, and the result is thus that 109 patients (44 per cent) had serious complaints at the time of follow up (Table XII)

Recurrence was found in five of the 239 patients in whom colpoperineorrhaphy had been performed There may also be

Table XI *Disturbances of Micturition (Except Incontinence) at the Time of Follow up Examination*

	No of Patients
Disturbances of micturition	
with recurrence of prolapse	15
with hypertrophy of cervix	2
no findings at examination	12
	29

Table XII *Disturbances at the Time of Follow up Examination (251 Patients)*

	No of Patients	%
Objective recurrence	73	29
Incontinence	19	8
Hypertrophy of cervix	5	2
Disturbances of micturition	12	5
	109	44

recurrences hidden among those who were not examined, as minor degrees of rectocele do not always produce symptoms

One hundred and ninety four of the operations were performed by the head of the department, while 57 were performed by his senior registrars (a total of seven during the period in question) Fifty eight and 15 recurrences respectively were found in these two groups of patients There is no significant difference in the recurrence incidence ($P > 0.2$)

Pregnancy did not occur in patients who were operated on before the menopause The patients were not questioned concerning dyspareunia

Discussion

This material is not selected the method being routine during the period of study The observation period is long being at least five years Eighty five per cent were followed up although only 44 % of these have been gynæcologically examined The remainder are all symptom free but gynæcological examination would probably reveal further recurrences in this group This however,

would only add to a rate of recurrence already the greatest since Krönig (Döderlein-Krönig, 1924) reported a recurrence rate of 33 per cent. We investigated the possibility of special factors in our material to explain the large number of recurrences. Parity might play a part, but there was a wide spread of recurrences in the parity groups, and furthermore, the parity distribution does not differ from that found in other series (Table V). Previous treatment is not a significant factor either, with 31 per cent recurrences (Table VI). Supplementary surgical intervention such as resection of the uterus or myomectomy produced a recurrence rate similar to that of series as a whole (37 patients with 14 recurrences (38 per cent), $P > 0.1$). The same applies to patients who developed cystitis postoperatively (Table II, $P > 0.1$). Those with postoperative infection had 64 per cent recurrences, which is for that matter statistically significant ($P < 0.001$), but the seven recurrences represent too small a figure to influence the overall incidence, and the incidence of infection is no greater than in corresponding series (Jacobsen *et al.*, 1961, Nielsen, 1954, Tophoj and Riber Christensen, 1959).

It has often been stated in defence of the interposition method that it is suitable in selected cases (Brady, 1953, Rosenfeld, 1953, Granjon and Chevalier, 1961). The criteria for selection vary from one author to the other, but on the whole there seems to be agreement that there should be preference for women before or just after the menopause, with prolapse of the uterus of first or second degree. The significance of age is difficult to evaluate in the present material, as the loss of patients was relatively great in the oldest age group, because of the long observation period. Among the survivors, however, there is no major difference in recurrence rate between age groups over or under 55 years of age, the figures being respectively 33 per cent and 26 per cent (Table XIII), ($P > 0.05$). On the other hand, the analysis confirms that the method is quite unsuitable for repairs of third degree prolapse, where a recurrence rate of 60 per cent was found. These two groups of patients, namely of high age and with severe degree of disease, always influence any postoperative survey unfavourably.

Table XIII *The Relation Between Recurrence and Age at Operation*

Years of Age	No of Patients	No of Recurrences	%
≤ 55	151	40	26
> 55	100	33	33

Unfortunately, the figures are rather small for the evaluation of the method for relief of incontinence, although they are of the same order of magnitude as those of Nabriski and Zeeloof These authors obtained complete cure in 29 of 45 patients (64 per cent), as compared with our results of 22 out of 44 (50 per cent) Tophøj and Riber Christensen had a total of 26 3 per cent with incontinence among their patients at follow up, the incontinence having appeared after operation in 10 per cent In our series, incontinence was never the sole indication for operation

The value of amputation of the cervix as a prophylactic measure against recurrence is not significant (five of 22 where amputation was performed developed recurrence (23 per cent, $P > 0\ 1$) two have even undergone reamputation at a later date) Kielland s method for elimination of the cervix was *not employed*, on the recommendation of Nilsen (1954) The latter s figures are however not statistically significant either

Throughout the years the interposition operation for prolapse of the uterus has been much debated, and feelings more than facts have often prevailed in the discussion Thus, Samuel Rosenfeld (1953) in an enthusiastic defence of the method, writes "I have no knowledge of even one complete failure without any *information* of whether the patients were followed up or not length of observation period etc Bradys (1953) claim for the method is based on a similarly unclear foundation Berger (1961) tabulated after K Arnold 28 reviews of patient series treated by interposition operations The size of these series varied from 31 to 836 patients with recurrence rates from one to 24 3 per cent

The best investigated series from recent years are presumably *those* of Tophoj and Riber Christensen (1959) and Nilsen (1954) where nearly all the patients are traced and

attended for gynæcological examination These authors found 6 3 and 13 5 per cent recurrences, respectively, with observation periods ranging from a few months to twelve years

With the use of the 'Manchester operation", which is the technique of choice in recent years, Hill and Hoog (1957), in a large and well-investigated series, found an objective recurrence rate of 24 1 per cent, but a subjective recurrence rate of only 6 8 per cent

There thus appears to be scope for continued disagreement, but on the basis of our experience we cannot recommend the method as a suitable routine procedure It may find employment in a restricted number of cases, provided special attention is paid to severe degrees of uterine prolapse, which should be considered as a contraindication

SUMMARY

During the period 1939–1956, the interposition method was used as routine in the surgical department B of the Diakonissestiftelsen Hospital, Copenhagen Two hundred and ninety-seven patients were operated on Follow up examination was completed in 251, by questionnaire in 141 (those patients without any symptoms), by gynæcological examination in 110 There were 73 recurrences (29 per cent), 13 with cystocele, 34 with prolapse of second degree, and 24 with prolapse of third degree In two cases, the recurrence could not be classified A further 37 patients had slight to moderate symptoms The period of observation extended from five to 21 years with an average of 12 3 years in the patients without recurrence Forty one per cent of the recurrences were within the first year after operation, the latest 21 years after

The value of the method for the treatment of true as well as stress incontinence cannot be estimated, as this symptom was never the only indication for operation No statistically significant difference was found between cases with and without amputation of the cervix (22 with five recurrences, against 229 with 68 recurrences)

There seems to be a tendency to aggravation of the prolapse

with recurrence 10 per cent had prolapse of the third degree before operation, whereas there were 33 per cent among the recurrences

The age at operation had no significant influence on the tendency to recurrence

The method cannot be recommended as a routine procedure and in our opinion it is of little value in repair of prolapse of the third degree

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INVASIVE CARCINOMA OF THE UTERINE CERVIX WITH SPECIAL REFERENCE TO ITS SURGICAL TREATMENT[1]

BY

M LANDGREEN G ILLEMANN LARSEN AND JOHAN IVERSEN

The rational treatment of invasive cervical carcinoma is still a matter for discussion Radiotherapy is favoured in the Scandinavian countries especially by Kottmeier who heads the *Stockholm school By individual assessment of dosage, this group* has obtained a 5-year survival of 76 per cent in Stages I and II a By surgical treatment of patients in the same stages August Christensen and his associates have been able to achieve a 5-year survival rate of 82 7 per cent in Stage I and of 55 8 per cent in Stage II Gorton, in a series treated by primary radio therapy and subsequent lymphadenectomy, obtained a 77 per cent 5-year survival in Stages I and II

At the 13th congress of Scandinavian gynæcologists in Lund, Sweden, on June 4–6, 1964, one of the main topics was the surgical and radiation treatment of invasive carcinoma of the uterine cervix (Acta Obstetricia et Gynecologica Vol XLIII, supplement 2, 1964) As was to be expected the proceedings did not bring any final elucidation of the problem

Present Series

At the above-mentioned congress we submitted the results obtained by surgery in the treatment of invasive cervical car-

[1] Read, in a modified form, at the 13th Congress of Scandinavian Gynæcologists in Lund, Sweden, 1964 by J I

Table I *Operations for Invasive Cervical Carcinoma Carried out in the Copenhagen County Hospital in Gentofte during the Period 1 9 1954–1 5 1964*

Surgical Procedure		Number of Deaths to Date
Radical surgery (Wertheim Meigs)	118	26
Radical surgery for recurrence following radiotherapy	5	1
Exenteration	1	1
Exploratory laparotomy (inoperable)	2	2
Amputation/excision of the cervix	4	1
Abdominal hysterectomy	9	1
Total	139	32

Table II *118 Patients with Invasive Cervical Carcinoma Treated Primarily by Surgery Listed by Year of Operation and Clinical Stage*

Year	Number of Cases	Stage I	Stage II
1954 (from 1 9)	6	4	2
1955	17	16	1
1956	13	12	1
1957	15	12	3
1958	19	17	2
1959	9	7	2
1960	9	8	1
1961	10	7	3
1962	12	10	2
1963	6	4	2
1964 (up to 1 5)	2	1	1
Total	118	98	20

cinoma at the Copenhagen County Hospital in Gentofte, Denmark

Table I lists the operations performed in the Department during the period 1 9 1954–1 5 1964 During this period of nearly 10 years a total of 139 operations were carried out The great majority (118 cases) were radical operations by the Meigs modi

Table III *Cases of Newly Diagnosed Cervical Carcinoma, Treatment and Age Grouping during the Period 1.9.1954–1.5.1964*

Patients treated surgically	133 (52.6%)
Referred for radiotherapy	120 (47.4%)

Age groups of surgically treated patients		*Age groups of patients referred for radiotherapy*	
< 45 years	86 (64.7%)	< 45 years	28 (23.3%)
45–55 years	38 (28.6%)	45–55 years	30 (25.0%)
> 55 years	9 (6.7%)	> 55 years	62 (51.7%)

Table IV *Reasons for Referring Patients for Radiotherapy—120 cases*

Stage I clinically operable	refused operation	1	4	120
	anaplastic carc.	1		
	an endocervical, large tumour, possibly Stage II	2		
Stage II, contra indications to surg.	advanced age	8	12	
	other diseases	4		
Stage II estimated as inoperable			68	
Stage III estimated as inoperable			32	
Ssage IV estimated as inoperable			4	

Table V *Number of Cases of Carcinoma Complicated by Pregnancy and of Stump Carcinoma in the Series*

8 cases of cervical carcinoma in pregnancy	7 had Meigs operation 1 died 1 treated by amputation of the cervix
3 cases of stump carcinoma (previous subtotal hysterectomy)	1 had Meigs operation 2 had excision of the cervix (one by the abdominal and the other by the vaginal approach)

referred for radiotherapy, but died with distant metastases 3 years later

Table VI *Pathological Classification in All Cases Having Radical Surgery*

Parakerat cervical carcinoma	98 patients
Solid cervical carcinoma	30 patients
Cervical adenocarcinoma	5 patients (3.8 %)

Table VII *Incidence of Pelvic Lymph Node Involvement*

Clinical Stage I	Out of 98 patients 13 had involved nodes (13.3 %)
Clinical Stage II	Out of 20 patients 10 had involved nodes (50.0 %)

Table VIII Disparity *between Clinical and Operative Staging of Cervical Carcinoma*

1 Died after a primary Meigs operation														
Clinical stage	Ia	Ia	Ia	Ia	Ib	Ib	Ib	Ib	Ib	II	II	II	II	
Stage found at operation	Ia	II	III	IV	Ia	Ib	II	III	IV	Ib	II	III	IV	Total
Number	0	0	0	0	0	9	1	7	0	2	3	3	1	26

2 Alive and well more than 5 years after a primary Meigs operation														
Clinical stage	Ia	Ia	Ia	Ia	Ib	Ib	Ib	Ib	Ib	II	II	II	II	
Stage found at operation	Ia	II	III	IV	Ia	Ib	II	III	IV	Ib	II	III	IV	Total
Number	7	0	0	0	1	32	8	1	0	0	2	3	0	54

fication of Wertheim's technique Lately, we have been using the method advocated by Okabayashi Certain technical modifications have not proved of any fundamental importance

Table II shows that the number of operations within the named 10 year period has been rather evenly distributed

Table III gives the total number of newly diagnosed cases of invasive cervical carcinoma the age distribution of the patients

All 5 patients in Stage I. One has died while the other 4 are still alive
1 died during the operation.

Table IX.

1. Number of Patients with > 5-Year Survival, Divided by Clinical Stages

	Number	Alive > 5 years	*
Stage I	63	49	77.7 %
Stage II	10	5	50.0 %

All 19 patients died of pelvic recurrence.

2. 5-Year Survival in Relation to Lymph Node Metastases

	No Metastases		Metastases	
	Number of cases	Surviving > 5 years	Number of cases	Surviving > 5 years
Stage I	55	46 (83.6 %)	8	3 (37.5 %)
Stage II	4	1 (25 %)	6	4 (66.7 %)

Table X. *Survival Time in Entire Series*

Follow-up Period	Alive	Dead	Total
> 5 years	54	19	73
3–5 »	15	4	19
1–3 »	19	2	21
< 1 year	4	1	5
	92	26	118

treated surgically and of the patients referred for radiotherapy. It is seen that the older age groups especially show a fairly large number at an inoperable stage, indicating delayed diagnosis. A total of 120 patients were referred for radiotherapy. The reasons are recorded in Table IV.

According to Table V, 8 patients had invasive cervical carcinoma complicated by pregnancy. Moreover, the series included 3 patients who had previously undergone subtotal hysterectomy for benign diseases. The treatment of these patients is listed. It must be added that one of the pregnant patients who had a

* 1 patient died during the operation. The other 25 died of pelvic recurrence.

Table XI *Patients Treated by Combined Surgery and Radiotherapy*

A. 118 patients treated primarily by Meigs operation

Postop X-ray irradiation 15 pts	12 with involved nodes (operat St III)	6 died; 6 alive: > 5 yrs 3, < 5 yrs 3
	imminent invasion, 3 parametrial infiltr, large tumour	all alive: 1 > 5 yrs, 2 < 5 yrs
Local recurrence	13 pts Radium Centre; 8 pts Later irrad	all died
3 pts	2 local recurrences in vaginal vault Radium Centre; 1 local recurrence in the vagina Irrad after excision	alive and well 2 > 5 yrs, 1 < 5 yrs

Table XII *Patients Treated by Combined Surgery and Radiotherapy*

B *Found to be inoperable at exploratory laparotomy*
2 pts Radium Centre — both died

C 1 pt with *requrrence following radiotherapy* (St IV) treated by anterior aed posterior exenteration — died 6 mo after the operation from intestinal fistula and local recurrence

D *Referred for operation* because of *radioresistance* or *recurrence during radiotherapy*

5 pts	Stage I 3; Stage II 2	all treated by Meigs operation	1 alive < 5 years postop; 3 alive > 5 years; 1 died of recurrence

E *Other operations*

2 pts had total hysterectomy	1 postop X ray therapy	Alive < 5 yrs
	1 X ray therapy after local recurrence	Died
1 pt excision of the cervix (vaginal repair)	Postop X-ray therapy	Died 3 years later (metast)

Table XIII *Surgical Technique*

Wertheim Meigs*	28
» » + circumcision and electrocoag of vagina	19
» » + » » » » » + drainage	11
» » + » » » » » + suction drainage	63
Okabayashi + suction drainage	2
Exenteration (bladder and rectum)	1
Other operations	18
Total	142

Table XIV *Operative Complications (123 Radical Operations)*

A *During operation*

1 pt died during the operation (hæmorrhage) 0 8 %

Others	profuse hæmorrhage	1	
	ureteral injury	2	
	bladder injury	3	1 e 7 3 %
	rectal injury	3	

B *Postop complications* (apart from fistulæ and strictures)

Severe cystopyelitis	10	Neurol (paresis of peroneus nerve)	1
Phlebitis	4	Paralytic ileus	1
Infarction	9	Abscess of abd scar	3
Abscess or hæmatoma in the pelvis	5	Vaginal bleeding	2

primary amputation of the cervix was later treated by hysterectomy without lymph node dissection (Stage I a)

The pathological classification of the tumours in the patients treated primarily by operation is recorded in Table VI

While the staging was based exclusively upon the gynæcological examination, the operative findings as well as microscopic study of the operative specimens often revealed a more advanced growth than was anticipated (Table VII) The positive nodal

* in 9 cases one ovary was left

Table XV *Postoperative Urinary Tract Fistulæ and Strictures*

Vesico-vaginal fistula	1	12 2 %
Unilateral uretero-vaginal fistula	7	
Vesico-vaginal + unilat. uretero-vaginal fistula	2	
Unilateral ureteral stricture	5	
Postop pyelographic changes persisting but no symptoms		5
" " " later disappeared no symptoms		17

Table XVI *Treatment of Fistulæ and Strictures*

Vesico-vaginal fistula	Lap with closing of the fistula anterior colporrhaphy with pubococcygeal reinforcement	1
Unilat uretero vaginal fistula	Lap with implant of ureter	2
	" " " " " + subsequent nephrectomy	1
	Spontaneous healing	3
	" " abolished renal function	1
Vesico-vaginal + unilat. uretero-vaginal fistula	Lap with implant of ureter + anterior colporrhaphy with pubococcygeal reinforcement	1
	Vaginal fist op + lap with implant. of ureter (died later of local recurrence)	1
Unilat ureteral strictures	Lap with implant of ureter	2
	Nephrectomy (one later died of recurrence)	2
	Lap with freeing of ureteral compression (died later of recurrence)	1
	Total	15

metastases were found in routine studies and thus represent minimum values

Similar findings are apparent from Table VIII in which the clinical stage is compared with the operation findings This comparison also shows that the growth is often more advanced than

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Conclusions

In our Department we have arrived at the following views regarding the problems connected with invasive cervical car cinoma

1 Invasive cervical carcinoma in Stage I a is preferably treated by abdominal total hysterectomy with removal of the uppermost part of the vagina
2 Invasive cervical carcinoma clinically classified as Stage I b and Stage I–II we consider suitable for extended surgery In such cases we now generally use the Okabayashi operation
3 Invasive cervical carcinoma classified clinically as Stage II is referred for radiotherapy, as the surgical findings often show that the growth is in fact more advanced than was assumed on the basis of the clinical preoperative assessment.
4 If the operation reveals a growth more advanced than assessed clinically (nodal metastases, etc), the surgical procedure is nevertheless carried through as planned and followed by postoperative X ray irradiation
5 Preoperative lymphangiography may perhaps disclose nodal metastases and thus contribute to a more exact preoperative staging

SUMMARY

During the period from 1 9 1954-1 5 1964 a total of 139 patients with invasive carcinoma of the uterine cervix were treated surgically in the Department of Gynæcology and Obstetrics the Copenhagen County Hospital in Gentofte

The majority (123) had the Wertheim Meigs operation Out of this group 118 were newly diagnosed—all assessed as primarily operable 98 being clinically estimated as Stage I and 20 as Stage II cases The remaining 5 patients had radioresistant tumours or recurrences following radiotherapy

In 16 cases the procedures were as follows Exenteration in 1 case total abdominal hysterectomy in 9 high excision of the cervix in 4 and exploratory laparotomy (showing that the cases were inoperable) in 2

Nodal metastases were demonstrated in 13 cases (13 3 per

originally assumed This applies to the patients who survived for less than 5 years after the operation as well as to the others

The survival time depends upon the stage of the disease at the commencement of treatment The results, assessed on the basis of the 5-year survival, are shown in Table IX which also gives the fate of patients with and without nodal metastases It must be pointed out, however, that the number of patients classified preoperatively as Stage II is small and does not permit firm conclusions Although the 5-year survival is the correct expression of the therapeutic efficacy, Table X states the fate of all patients operated upon during the 10-year period and followed up to date

As mentioned in the introduction, Gorton recommends combined surgery and radiotherapy This procedure has been used by us in selected cases who had postoperative radiotherapy (Tables XI and XII) In cases where the operation revealed a more advanced growth than was assumed clinically, the operation was carried through as planned

Certain minor technical modifications were, as mentioned above, of no fundamental significance These modifications are listed in Table XIII Electrocircumcision of the vagina was performed introductory to the operation on the basis of views concerning the course of the lymphatics and their role in subsequent recurrence in the vaginal vault It must be mentioned that suction drainage proved of the utmost importance, and after we started using it we have not had any complications worth mentioning in the true pelvis Our reason for later changing to the Okabayashi method is that in our opinion this procedure is technically easier, especially in freeing the ureter

In assessing the value of a method, regard must be paid also to the complications which may arise during the operation as well as postoperatively Table XIV lists the postoperative complications apart from the urinary tract fistulæ and ureteral strictures which are shown in Table XV These complications are the price which has to be paid for obtaining an otherwise favourable result The incidence does not differ appreciably from that reported by others The treatment of the complications is recorded in Table XVI

Conclusions

In our Department we have arrived at the following views regarding the problems connected with invasive cervical carcinoma

1 Invasive cervical carcinoma in Stage I a is preferably treated by abdominal total hysterectomy with removal of the upper most part of the vagina
2 Invasive cervical carcinoma clinically classified as Stage I b and Stage I–II we consider suitable for extended surgery In such cases we now generally use the Okabayashi operation
3 Invasive cervical carcinoma classified clinically as Stage II is referred for radiotherapy, as the surgical findings often show that the growth is in fact more advanced than was assumed on the basis of the clinical, preoperative assessment
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cent) of those who had been assessed preoperatively as Stage I and in 10 (50 per cent) of those assessed as Stage II

Eight patients were pregnant and 3 had tumours of the cervical stump following subtotal hysterectomy

Twenty-six of the surgically treated patients have died, one died during the operation (of hæmorrhage) and 25 have succumbed to recurrences

In 73 cases the operation was performed more than 5 years ago Of these patients 54 (74 per cent) are alive and clinically well, while 19 have died

Fifteen patients with nodal metastases received postoperative radiotherapy, 9 are still alive Twenty-four patients with recurrences had radiotherapy, 3 have survived

The surgical technique was the Wertheim-Meigs operation with slight modifications (electrocircumcision of the vaginal walls and abdominal suction drainage) Later, the Okabayashi method was adopted, as it seems to be technically easier

The primary mortality was 0 8 per cent Fistulæ and strictures of the urinary tract occurred in 12 2 per cent All the fistulæ healed spontaneously or were closed surgically In 3 cases nephrectomy had to be performed There were no other serious postoperative complications

Apart from the above-mentioned cases, another 120 patients with invasive carcinoma of the cervix were referred for radiotherapy, as they were in a more advanced stage of their disease

The conclusions drawn from the experience gained in our Department are as follows

1 Invasive cervical carcinoma in Stage I a is preferably treated by abdominal total hysterectomy with removal of the uppermost part of the vagina
2 Invasive cervical carcinoma in Stages I b and Stage I–II is considered suitable for extended surgery (Wertheim-Meigs or Okabayashi)
3 Invasive cervical carcinoma classified clinically as Stage II is best referred for radiotherapy, as the surgical findings often show that the growth is in fact more advanced than assumed on the basis of the clinical, preoperative findings
4 If the operation reveals a growth more advanced than as-

sessed clinically, the surgical procedure is nevertheless performed and followed by postoperative X ray irradiation

5 Preoperative lymphangiography may perhaps contribute to a more exact preoperative staging by revealing nodal metastases This procedure has recently been introduced in our radiological department

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